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Comparison of Major Molecular Responses Achieved at 12 Months with Imatinib Versus Newer Generation Tyrosine Kinase Inhibitors in Philadelphia Chromosome Positive Chronic Myeloid Leukemia Patients: A Systematic Umbrella Review and a Meta-analysis

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Abstract

Background: Chronic myeloid leukemia is myeloproliferative disorder that arise due to overexpression of ABL tyrosine kinase enzyme as a result of fusion of ABL gene on chromosome 9 to BCR on chromosome 22. This leads to neoplastic proliferation of myeloid stem cells. It is treated with BCR-ABL Tyrosine kinase inhibitors. Efficacy is measured using Major molecular response. MMR is reached if the standardized BCR-ABL: ABL gene ratio less than 0.1% in blood or bone marrow. The faster MMR is reached the faster the recovery.

Objective: To compare major molecular response at 12 months achieved with the use of first versus newer generation Tyrosine Kinase Inhibitors in Philadelphia (9:22 translocation) chromosome positive Chronic myeloid leukemia, utilizing an Umbrella review of existing papers on the topic.

Methodology: An Umbrella review and a meta-analysis were performed on meta-analysis conducted, comparing MMR at 12 months with Imatinib vs new generation TKIs. PubMed and Mendeley search engine were used to search for meta-analysis published on the afore mentioned topic. Their results (Risk ratio of MMR 12) were pooled to produce an overall result. Publication bias and forest plot were drawn. Quality assessment of studies included was performed using AMSTAR2 tool. PRISMA flow diagram was also drawn to simplify the search and screening strategy. Protocols were registered at Open science framework. Research was self-funded.

Results:3 studies met the inclusion exclusion criteria. The proportion of patients achieving MMR with Newer generation Tyrosine kinase inhibitors were greater than those with First generation (Imatinib), RR: 1.58 CI: 1.49, 1.68.

Conclusion: Newer generation TKIs are better in achieving MMR at 12 months than Imatinib.

Keywords: Efficacy of Tyrosine kinase inhibitors in CML, Imatinib adverse effects in CML

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Introduction

Chronic myeloid leukemia is myeloproliferative disorder that arise due to overexpression of ABL tyrosine kinase enzyme as a result of fusion of ABL gene on chromosome 9 to BCR on chromosome 22. This leads to neoplastic proliferation of myeloid stem cells. It is treated with BCR-ABL Tyrosine kinase inhibitors. Efficacy is measured using Major molecular response (MMR). MMR is reached if the standardized BCR-ABL: ABL gene ratio less than 0.1% in blood or bone marrow. The faster MMR is reached, the faster the recovery. Chronic myeloid leukemia is treated with Tyrosine kinase inhibitors. There are 3 generations of TKIs, e.g. first generation (Imatinib), second generation (Dasatinib, Nilotinib) and third generation (Ponatinib). [1] Molecular response is the measure of BCR-ABL RNA in the blood or bone marrow, the lower it is the better the outcome for patients. A major molecular response simply means that the ratio of translocated BCR-ABL to Normal ABL gene is less than 0.1%. [2-5] Many studies have concluded that newer generation TKIs like ponatinib are more efficacious in achieving MMR in more patients as compared to imatinib. This comes with its side effects, e.g. thrombocytopenia, neutropenia, rash, cardiovascular, cerebrovascular and peripheral vascular adverse events etc. [6]

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Methodology

The PICO (Population, Intervention, Comparison and Outcome) entities performed in this paper were the following:

- Patients: 9:22t positive CML patients.
- Intervention: Imatinib, irrespective of dose.
- Comparison: Ponatinib, irrespective of dose.
- Outcome; Risk Ratio of Molecular responses at 12 months.

Author 1 searched PubMed and Mendeley search engine for meta-analysis from January 10 through 11 January 2025. Only meta-analysis of randomized control trials (RCT)were included. Paid articles were excluded. Language of the included articles was limited to English. Only those Meta-analysis were included, that measured the effect size in terms of Risk Ratio.

The following search terms were used:

- PubMed: (("imatinib mesylate"[MeSH Terms] OR ("imatinib"[All Fields] AND "mesylate"[All Fields]) OR "imatinib mesylate"[All Fields] OR "imatinib"[All Fields] OR "imatinib s"[All Fields]) AND ("ponatinib"[Supplementary Concept] OR "ponatinib"[All Fields]) AND ("chronic myeloid leukaemia"[All Fields] OR "leukemia, myelogenous, chronic, bcrabl positive"[MeSH Terms] OR ("leukemia"[All Fields] AND "myelogenous"[All Fields] AND "chronic"[All Fields] AND "bcrabl"[All Fields] AND "positive"[All Fields]) OR "bcr-abl positive chronic myelogenous leukemia"[All Fields] OR ("chronic"[All Fields] AND "myeloid"[All Fields] AND "leukemia"[All Fields]) OR "chronic myeloid leukemia"[All Fields])) AND (meta-analysis[Filter]).
- Mendeley: Imatinib AND Ponatinib AND Chronic myeloid leukemia.

The results were merged and then de-duplicated 2 times using SR accelerator automation tool, once before screening the results for meta-analysis (via Rayyan, an AI automation tool) and once after. [1]Following this the results were screened using PICO criteria. Only publicly available (free/open access) and those published in English language were included. Note that PubMed allows user to filter results base on type of articles (review, trial etc.) but Mendeley does not, hence the search results of both search engines were combined and filtered using Rayyan. Literature was screened by author 1. Prisma Flow diagram has also been given in Figure 1 to simplify this. Characteristics of the studies included is given in Table I.

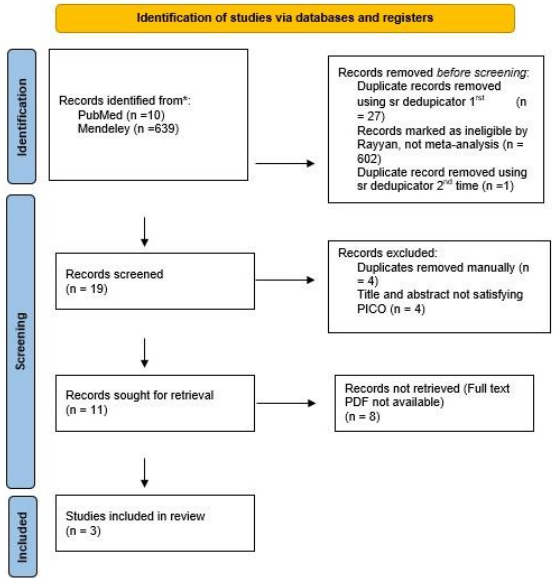

Figure 1. Prisma flow diagram for identification of studies via databases and registers.

SERIAL NO. 1	
Table I: Characteristics of studies included	
Author(s)	Zhe Wang et al
Year of publication	2016
Journal	*JAMA Open Network: Hematology*
Protocol registration	PROSPERO: CRD42020202337.
Outcome evaluated	Primary: hepatotoxicity, including grade 3 and 4 ALT/AST elevation Secondary: Overall Survival and MMR at 12 months.
No. of RCTs included	9
No. of RCTs, whom RR of MMR at 12months were pooled	9
Total events + Total participants in Imatinib group	401+1,629
Total events + Total participants in new gen. TKIs group	754+1,356
Heterogeneity of pooled MMR at 12 Months	Heterogeneity: $\chi 2 = 9.28$; $df = 8$ ($P = .32$); $I2 = 14\%$ Note: Insignificant heterogeneity
SERIAL NO. 2	

Author(s)	Claudia Verner et al
Year of publication	2020
Journal	*Blood Advances*
Protocol registration	PROSPERO; registration no. CRD42016032903
Outcome evaluated	Primary: OS, Progression Free Survival Secondary: Complete Cytogenic Response at 3 12 24 36 48 60 months, Early Molecular Response at 3 months, MMR at 3 12 24 36 48 months, MR4, MR4.5, Transformation to Acute Phase and Blast Phase CML, discontinuation of treatment
No. of RCTs included	7
No. of RCTs, whom RR of MMR at 12months were pooled	6
Total events + Total participants in Imatinib group	Not mentioned, only total number of patients= 2,208
Total events + Total participants in new gen. TKIs group	Not mentioned, only total number of patients= 2,208
Heterogeneity of pooled MMR at 12 Months	Not mentioned
SERIAL NO. 3	
Author(s)	Ronit Gurion et al.
Year of publication	2021
Journal	*Acta Oncologica*
Protocol registration	None
Outcome evaluated	Primary: MMR and CMR at 12 months Secondary: CCyR at 12, MMR at 3 18 24 48 months, Complete Molecular Response at 24 months, Transformation to AP BP at 12 18 24 60 months, all-cause mortality at 12 24 months and 3-5 years.
No. of RCTs included	8
No. of RCTs, whom RR of MMR at 12months were pooled	8
Total events + Total participants in Imatinib group	474 + 1,504
Total events + Total participants in new gen. TKIs group	869 + 1,779
Heterogeneity of pooled MMR at 12 Months	Heterogeneity: chi^2=13.01, df= 7, p=0.07, I^2=46% Note: Significant heterogeneity

AMSTAR 2 quality assessment tool was used to perform Risk of bias assessment on the included 3 studies by Author 2 and Author 1[2]. Final decision was made by Author 1. AMSTAR 2 is a tool made by Joanna Briggs Institute for quality assessment of Systematic reviews and meta-analysis. It consists of 16 domains/questions/items that can be answered as YES, NO and/or Partial Yes. Item number 2, 4, 7, 9, 11, 13, 15 are critical domains. Quality of the study is classified as high, moderate, low and critically low based on the numbers of negatively (NO) answered critical domains. Quality assessment results given in Table II.

Table II: AMSTAR-2 tabulated data.

Item #	**Gurion 2016**	**Vener 2020**	**Wang 2021**
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
No. of critical domains weaknesses (negatively answered)	1	2	1
Final rating	Low	Critically low	Low

Key
- Yes
- Partial yes
- No

Key: High value: 0-1. noncritical weakness;Moderate value: > 1. noncritical weakness. The systematic review has more than one weakness, but no critical flaws;Low value: 1. critical flaw with or without noncritical weakness;Critically low value: > 1. critical flaw with or without noncritical weakness.

For publication bias, a funnel plot has been included

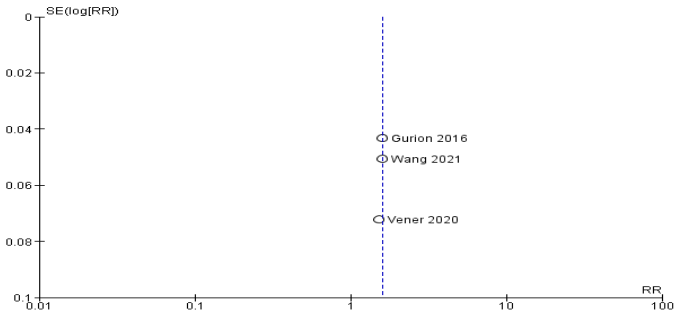

Figure 2. Funnel plot for publication bias

Y axis shows standardized error and X axis shows Risk ratios of individual studies. Asymmetrical distribution of studies across the line of pooled effect size means that there is publication bias, as it is not possible to visually interpret the results of the funnel plot so a statistical test (Egger's regression test) is given to solve the problem.

All statistical analysis was performed using Revman 5.4 by Author 1. [3] The results of all 3 meta-analysis were pooled using random affects model. A funnel plot was drawn to find the publication bias. Egger's regression test was also performed to asses publication bias using MS Excel. As Only 3 studies met the inclusion/exclusion criteria, therefore sensitivity analysis was not performed even though 2 articles had low rating and 1 had Critically low rating in quality assessment. A sensitivity analysis is performed by removing studies with potential bias from the forest plot to find out which study is the cause of the heterogeneity. In our study the heterogeneity was Zero (P>0.05) even though studies included had bias. Funnel plot is given in Figure 2, Forest plot in Figure 3 and Egger's regression in Table III.

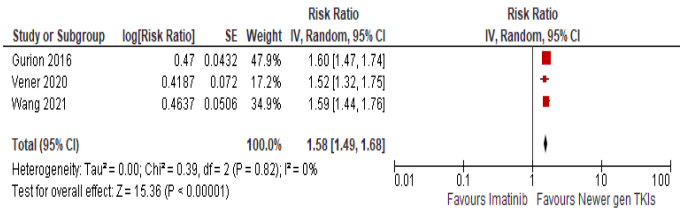

Figure 3. Forest plot for risk ratios for MMR at 12 months.

Results

A total of 649 studies were retrieved, viz. PubMed=10 and Mendeley=639. Records retrieved after initial deduplication (using SR accelerator) were 622. Following this, studies were filtered using Rayyan to exclude non-meta-analysis.[4] 20 studies were retrieved, which were again de-duplicated. 1 duplicated study was removed this time. The 19 studies that were retrieved, these were screened for duplicates, this time manually using EndNote and 4 were removed, 4 studies did not fit the PICO criteria and were removed.[5] 11 articles were left, of which were searched to find Full text articles. Only 3 articles were retrieved, others were either paid to access or simply not accessible to the authors. A Prisma flow diagram is included for identification of studies via databases and registers.[6]

Table III: Egger's regression test results for publication bias.

Regression Statistics		ANOVA	
Multiple R	0.990899	Value	Regression
R Square	0.98188	df	1
Adjusted R Square	0.96376	F	54.1875
Standard Error	0.002847	F significance	0.085957
Observations	3		
R Square	0.98188		
Egger's regression, Intercept (P=0.077997)			
Coefficients	Confidence Interval	*Standard Error*	Confidence Interval
0.589067	-0.33256 to 1.510696	0.072534	-0.33256 to 1.510696

Egger' regression test was also performed utilizing standard errors on the Y axis and risk ratio on the X axis:

Null hypothesis for Egger's test is that there is no publication bias and the intercept is 0, with a p-value >0.05. Here the intercept is 0.589 with a p-value of 0.077 (>0.05). Here the value is greater than 0.05 hence there is NO publication bias.A forest plot has been included, indicating MMR at 12 months at with first vs newer generation TKIs. Note that random effect model was used:

In meta-analysis conducted by Ronit, Gurion et al[7] the risk ratio of MMR at 12 months were in favor of new generation TKIs (RR: 1.60, CI: 1.47, 1.74), 474 patients out of 1504 treated with Imatinib developed MMR at 12 months as compared to 869 out of 1779 treated with new generation Tyrosine kinase inhibitors. Similar results were reported by Claudia, Vener et al RR: 1.52, CI: 1.32, 1.75 and Wang, Zhe et al RR: 1.59 CI: 1.44, 1.76 (401 out of 1629 patients in Imatinib group and 754 out of 1356 patients in new generation TKIs group achieved MMR at 12 months). [8,9] The pooled results of our meta-analysis were also in favor of new generation TKIs, RR: 1.58 CI: 1.49, 1.76. meta-analysis conducted by

Gurion added the highest (47.9%) weight to our study. There was no heterogeneity in our meta-analysis as Tau^2=0.00.

Discussion

In the meta-analysis performed by Zhe Whang et al, 9 RCTs were included.[9] The secondary outcome included MMR at 12months. All 9 RCTs included this particular secondary outcome. The Risk ratio were calculated for all 9 RCTs and were pooled together using a forest plot.In the meta-analysis performed by Claudia Vener et al, 7 RCTs were included. The primary outcome included MMR at 12 months. Only 6 RCTs included this particular outcome. The Risk ratio were calculated for all 6 RCTs and were pooled together using a forest plot.[8]In the meta-analysis performed by Ronit Gurion et al, 8 RCTs were included. The secondary outcome included MMR at 12 months. All 8 RCTs included this particular outcome. The Risk ratio were calculated for all 8 RCTs and were pooled together using a forest plot.[7]

We pooled the Risk ratios for MMR at 12 months for all 3 included studies and the results clearly indicates that newer generation of Tyrosine Kinase inhibitors achieve MMR at 12 months in greater number of patients than Imatinib (first generation TKIs).

In a network meta-analysis conducted by Mealing et al, the odds ratio of MMR at 12 months for Dasatinib and Nilotinib (second generation TKIs) were 2 time higher than Imatinib 400mg, with Imatinib 400mg being the reference category OR for dasatinib 100mg was 2.09, OR for Nilotinib 300g was 2.87.[10] This also clearly shows that greater number of patients achieve MMR at 12 months with new generation TKIs as compared to Imatinib. New generation of TKIs are better in preventing Acute/Blast phase transformation but have increase probability to cause adverse events and elevate liver enzymes namely AST and ALT.[8,9,10]It can be said that imatinib should be preferred in patients with co-morbidities while newer generation of TKIs should be preferred in patients without co-morbidity. Treatment free remission is also a concern. In a retrospective study conducted by Ameer Aleem et al, only 27.3% out of 45 patients relapsed after discontinuing TKIs following the achievement of Deep molecular response, with the medium time to relapse being 5 months (range 2-38). In this study 52.7% of the patients were receiving imatinib at the time of discontinuation. It should be noted that while the study reports TFR in about 2/3 of the population after a median follow up of 24 months, the study is limited by its retrospective design.[11]

Conclusion

This systematic review and meta-analysis conclude that newer generation TKIs (second and third) are better than Imatinib (first generation TKIs) in achieving major molecular responses at 12 months in chronic myeloid leukemia patients.

References

1. Forbes C, Greenwood H, Carter M, Clark J. Automation of duplicate record detection for systematic reviews: Deduplicator. *Systematic Reviews*. 2024 2;13(1):206.doi: https://doi.org/10.1186/s13643-024-02619-9.
2. Shea BJ, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358. doi: https://doi.org/10.1136/bmj.j4008.
3. Review Manager 5 (RevMan 5) [Computer program]. Version 5.4. Copenhagen: The Cochrane Collaboration, 2020.
4. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan - a web and mobile app for systematic reviews. *Systematic Reviews*. 2016;5:1-0.doi: https://doi.org/10.1186/s13643-016-0384-4.
5. The EndNote Team (2013). EndNote. Philadelphia, PA, Clarivate
6. Page MJ, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372. doi: https://doi.org/10.1136/bmj.n71.
7. Gurion R, Raanani P, Vidal L, Leader A, Gafter-Gvili A. First line treatment with newer tyrosine kinase inhibitors in chronic myeloid leukemia associated with deep and durable molecular response–systematic review and meta-analysis. *Acta Oncologica*. 201;55(9-10):1077-83.doi: 10.1080/0284186X.2016.1201214.
8. Vener, C., et al. (2020). First-line imatinib vs second- and third-generation TKIs for chronic-phase CML: a systematic review and meta-analysis. Doi: https://doi.org/10.1080/0284186X.2016.1201214
9. Mealing S, Barcena L, Hawkins N, Clark J, Eaton V, Hirji I, Davis C. The relative efficacy of imatinib, dasatinib and nilotinib for newly diagnosed chronic myeloid leukemia: a systematic review and network meta-analysis. *Experimental Hematology & Oncology*. 2013;2:1-9. doi: https://doi.org/10.1186/2162-3619-2-5
10. Mulas O, Caocci G, Mola B, La Nasa G. Arterial hypertension and tyrosine kinase inhibitors in chronic myeloid leukemia: a systematic review and meta-analysis. Frontiers in Pharmacology. 2021 Sep 22;12:674748. doi: https://doi.org/10.3389/fphar.2021.674748.
11. Aleem A et al. Discontinuation of tyrosine kinase inhibitor therapy and treatment free remission (TFR) in chronic myeloid leukemia: Successful achievement of TFR in more than two-third of patients in a real-world practice. *Clinical Lymphoma Myeloma and Leukemia*. 2025;25(1):50-6. doi: https://doi.org/10.1016/j.clml.2024.08.006.