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ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

Major molecular responses in newly diagnosed chronic myeloid leukemia
A meta-analysis of one-year outcomes of dasatinib, imatinib, and nilotinib treatments

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2025, 42(5):652–659

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OBJECTIVE **To assess the effectiveness of imatinib, dasatinib, and nilotinib in achieving a major molecular response at 12 months (MMR12) as first-line treatments for chronic phase chronic myeloid leukemia (CML).** METHOD **A meta-analysis was performed utilizing data extracted from PubMed, Embase, and Scopus, covering the period from May to June 2024. Information on MMR12 from each study was compiled to estimate effect sizes using the Mantel-Haenszel method. The statistical analysis was conducted with Review Manager 5.1.** RESULTS **The analysis included a total of 27 articles. Our findings indicated that dasatinib exhibited higher efficacy in achieving MMR12 compared to imatinib (odds ratio [OR]: 2.03; 95% confidence interval [CI]: 1.77–2.32; p<0.0001). Additionally, nilotinib was found to be more effective than imatinib for treating chronic phase CML (OR: 2.75; 95% CI: 2.41–3.18; p<0.0001). However, dasatinib and nilotinib showed similar outcomes in the treatment of CML patients (OR: 0.74; 95% CI: 0.52–1.05; p=0.0900).** CONCLUSIONS **Dasatinib and nilotinib exhibit the most promising efficacy as first-line treatments for chronic phase CML based on the achievement of MMR12.**

Μείζονες μοριακές απαντήσεις στη νεοδιαγνωσθείσα χρόνια μυελογενή λευχαιμία: Μια μετα-ανάλυση της πορείας μετά από θεραπεία ενός έτους με δασατινίμπη, ιματινίμπη και νιλοτινίμπη

Περίληψη στο τέλος του άρθρου

Key words

Chronic myeloid leukemia
Dasatinib
Imatinib
Major molecular response at 12 months
Nilotinib

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Chronic myeloid leukemia (CML) continues to be a major health concern. The prevalence of CML has been projected to increase significantly, with estimates of approximately 70,000 cases in 2010, 112,000 in 2020, 144,000 in 2030, 167,000 in 2040, and reaching around 181,000 by 2050, where it is anticipated to approach a near-plateau prevalence.[1] The age-adjusted mortality rate for CML stands at 0.3 per 100,000 individuals per year. Mortality rates are notably higher among older adults, with the highest rates observed in those aged 75–84 years.[2,3] The management of CML, particularly in newly diagnosed patients, presents complex challenges. The selection of an appropriate tyrosine kinase inhibitor (TKI) requires careful consideration of various factors, including the specific treatment objectives, disease risk stratification, associated costs, and the presence of comorbid conditions.[4] The decision-making process for choosing the most effective TKI remains challenging due to the absence of clear and definitive evidence regarding the relative outcomes of these therapies. Consequently, there is a need for a comprehensive discussion and evaluation of the front-line treatment strategies for CML to improve patient outcomes and inform clinical practice.

Front-line therapy for CML presents ongoing challenges in its management. According to current clinical guidelines, the recommended first-line TKIs are imatinib, dasatinib, and nilotinib, each of which has been approved by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[5] Despite these recommendations, the selection of the most effective TKI remains a topic of debate, influenced by varying evidence. The DASISION study, a phase 3 randomized trial, reported that dasatinib exhibited superior efficacy compared to imatinib within the first year of therapy, including a significantly higher rate of major molecular response at 12 months (MMR12).[6] In contrast, long-term data from the IRIS trial and CML study IV, each extending beyond a decade of follow-up, demonstrated that imatinib's long-term ef-

ficacy remains unmatched by newer agents.[7] Moreover, a comprehensive review of existing literature suggested that dasatinib 100 mg, nilotinib 800 mg, nilotinib 600 mg were comparable in achieving complete cytogenetic and MMR12.[8] Conceptual distinctions in the mechanisms of action among dasatinib, nilotinib, and imatinib relate to their binding conformations and potencies. Dasatinib's ability to bind to the active conformation and its higher potency offer advantages against resistant mutations, whereas nilotinib's enhanced fit in the ABL kinase pocket provides superior efficacy against resistant mutations compared to imatinib.[9,10] Given the ongoing controversies regarding the optimal choice of front-line treatment for CML, a meta-analysis directly comparing these therapies was warranted to clarify their relative effectiveness.

MATERIAL AND METHOD

Design

The meta-analysis was designed to be conducted between May 1 and June 30, 2024. To achieve the research objectives, data extracted from each article were collected and analyzed to assess the cumulative odd ratio (OR) and 95% confidence interval (95% CI). The protocols were guided by a checklist based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, ensuring methodological rigor and transparency.[11] This meta-analysis has been registered with PROSPERO, with the registration number 562697.

Eligibility criteria

The eligibility criteria for this meta-analysis included both inclusion and exclusion parameters to ensure the selection of relevant and high-quality studies. The inclusion criteria specified that studies had to be either randomized controlled trials (RCTs) or observational studies, focus on evaluating the effects of dasatinib, imatinib, and nilotinib on MMR12 in patients with CML in the chronic phase, and have complete data for calculating cumulative effect estimates. The exclusion criteria involved eliminating studies that were irrelevant based on their title and or abstract, articles that were reviews or commentaries, and those of poor quality as determined by the Newcastle-Ottawa Scale for non-RCT papers or the Jadad modified scale for RCT papers.

Quality assessment

The articles were evaluated using specific tools: the Newcastle-Ottawa Scale for non-RCT articles and the Jadad modified scale for RCT articles. These tools assessed various components of the articles, including selection, comparability, and exposure for the Newcastle-Ottawa Scale, and randomization, blinding, and withdrawals for the Jadad modified scale. The measurement tools had defined minimum and maximum scores, with the Newcastle-Ottawa Scale ranging from 0 to 9 and the Jadad scale from 0 to 5. Scores were interpreted as follows: Low quality (0–3 for Newcastle-Ottawa, 0–1 for Jadad), moderate quality (4–6 for Newcastle-Ottawa, 2–3 for Jadad), and high quality (7–9 for Newcastle-Ottawa, 4–5 for Jadad).[12,13] The assessment of the articles' quality was conducted by FW.

Search strategy

The search strategy for the meta-analysis involved using several source databases, including PubMed, Embase, and Scopus. The search included articles published up to June 5, 2024, and was restricted to publications in English. The key words used in the search were "CML" and "MMR12" or "Major Molecular Response 12" and "imatinib" and "dasatinib" and "nilotinib." Additionally, relevant articles were identified by reviewing the reference lists of related studies to ensure a comprehensive collection of pertinent literature.

Data extraction

Information extraction from each article included capturing details such as the name of the primary author, year of release, country of origin for the study, study design, participants' age, CML phase, outcome measures, and sample sizes of both cases and controls. The data extraction process was conducted by FW. This systematic approach ensured that all relevant data points were gathered consistently across the selected studies, facilitating thorough analysis and comparison within the meta-analysis.

Covariates

The predictor covariates analyzed in this study were nilotinib, imatinib, and dasatinib, focusing on their effects within the context of CML in the newly diagnosed chronic phase. Specifically, the outcome covariate assessed was MMR12. This approach allowed for a comprehensive examination of how these treatments influenced the achievement of MMR12 in patients with newly diagnosed CML at the chronic phase.

Statistical analysis

The data presentation in this study was formatted as n (%), providing a clear representation of frequencies and percentages for the variables analyzed. To assess potential publication bias, both Egger's test and funnel plot asymmetry were employed. Publication bias was considered present if Egger's p-value was less than 0.05 or if the funnel plot showed asymmetry. Heterogeneity among studies was evaluated using the p-value for heterogeneity (p heterogeneity).[14] When substantial heterogeneity was observed, a random-effects model was utilized; in the absence of significant heterogeneity, a fixed-effects model was employed.[15] The main findings were assessed using the Mantel-Haenszel test, with a significance cutoff of $p<0.05$, indicating statistical significance.[16]

Review Manager 5.1 software was utilized for data analysis and presentation in this meta-analysis.

RESULTS

Study selection

In our systematic review, we initiated a comprehensive search of PubMed, Embase, and Scopus databases, yielding an initial total of 1,183 articles. Additionally, five articles were identified through the reference lists of related studies. After eliminating 12 duplicates and excluding 1,137 articles based on non-relevant titles and abstracts, 39 articles were subjected to a full-text review. Of these, five were excluded due to insufficient data and seven were excluded as they were review articles, resulting in a final inclusion of 27 articles for our study.[17–40] A detailed visual representation of the article selection process is provided in figure 1, and table 1 presents an overview of the baseline characteristics of the studies included.

The impact of imatinib, dasatinib, and nilotinib on major molecular response at 12 months in chronic phase CML patients

In our analysis, which included a total sample of 3,894 participants, we found that dasatinib might exhibit superior efficacy compared to imatinib (OR: 2.03; 95% CI: 1.77–2.32; p Egger: 0.3234; p heterogeneity: 0.3550; p<0.0001) (fig. 2A). Similarly, in the comparison between nilotinib and imatinib with a total sample of 3,812 participants, nilotinib potentially offered greater efficacy than imatinib (OR: 2.75; 95% CI: 2.41–3.18; p Egger: 0.2376; p heterogeneity: 0.9500; p<0.0001) (fig. 2B). However, in the comparison of dasatinib versus nilotinib with a total sample size of 653 participants, no significant difference was detected between the two treatments (OR: 0.74; 95% CI: 0.52–1.05; p Egger: 0.0643; p heterogeneity: 0.3000; p: 0.0900) (fig. 2C).

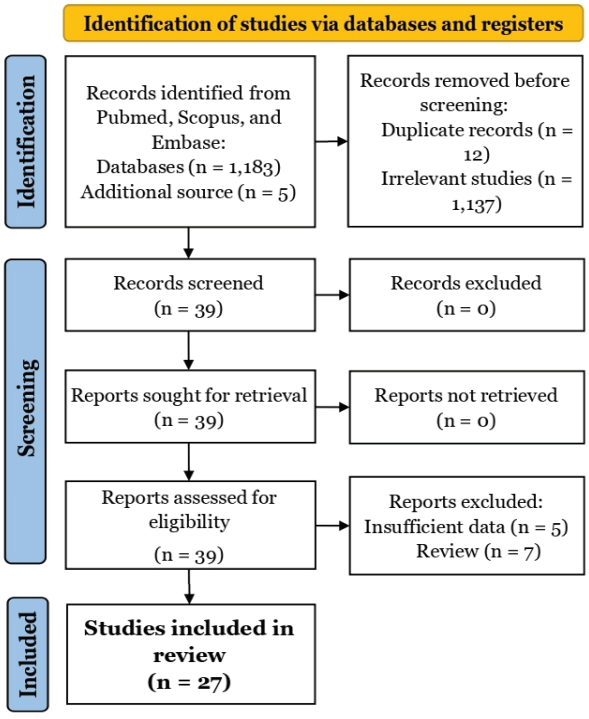

Figure 1. A flowchart of article selection.

Heterogeneity among studies and potential publication bias

In our examination of heterogeneity among studies and potential publication bias for various comparisons of TKIs, we found the following: For the comparison of dasatinib versus imatinib, the p-value for heterogeneity was 0.3550, indicating minimal variability among the studies and supporting the application of a fixed-effects model. Additionally, Egger's test yielded a p-value of 0.3234, suggesting no significant publication bias. In the comparison of nilotinib versus imatinib, the heterogeneity p-value was 0.9500, reflecting negligible heterogeneity and further justifying the use of a fixed-effects model. The p-value from Egger's test was 0.2376, indicating the absence of significant publication bias. Lastly, for the comparison of dasatinib versus nilotinib, the p-value for heterogeneity was 0.3000, also supporting a fixed-effects model due to low heterogeneity. Furthermore, the p-value from Egger's test was 0.0643, suggesting no evidence of publication bias (tab. 2).

DISCUSSION

Our findings revealed that dasatinib and imatinib exhibited better efficacy for achieving MMR12 compared to imatinib in the treatment of chronic phase CML. This meta-analysis was the first to compare dasatinib, nilotinib, and imatinib for chronic phase CML treatment. As such, we could not directly compare our results with previous studies. However, several studies have evaluated similar contexts, such as newer TKIs versus imatinib,[41,42] and indirect comparisons (Gurion, 2016).[8,43–45] These studies indicated that newer TKIs showed better efficacy in terms of early molecular response compared to imatinib for chronic phase CML.[41,42] Other studies, through indirect comparison, found that during the first year of treatment, nilotinib was associated with the highest MMR12 rate compared to

Table 1. Baseline characteristics of studies included in our analysis.

Study	Country	Design	Age	Sample size	Sub-type	Outcomes	Quality assessment
Dasatinib vs imatinib							
Fujisawa et al[18]	Japan	RCT	56	519	CML chronic phase	CCyR, MMR	Moderate
Hjorth-Hansen et al[25]	Norway	RCT	56	46	CML chronic phase	CCyR, MMR	Moderate
Hughes et al[19]	Australia	RCT	NA	35	CML chronic phase	CCyR, MMR	Moderate
Jabbour et al[20]	US	RCT	NA	519	CML chronic phase	CCyR, MMR	Moderate
Jain et al[24]	US	RCT	49	163	CML chronic phase	CCyR, MMR	Moderate
Kantarjian et al[21]	US	RCT	46	519	CML chronic phase	CCyR, MMR	Moderate
Kantarjian et al[35]	US	RCT	46	519	CML chronic phase	CCyR, MMR	Moderate
Nakamae et al[22]	Japan	RCT	NA	516	CML chronic phase	CCyR, MMR	Moderate
O'Brien et al[23]	UK	RCT	NA	812	CML chronic phase	CCyR, MMR	Moderate
Radich et al[17]	US	RCT	58	246	CML chronic phase	CCyR, MMR	Moderate
Nilotinib vs imatinib							
Hochhaus et al[31]	Germany	RCT	NA	286	CML chronic phase	CCyR, MMR	Moderate
Jain et al[24]	US	RCT	49	161	CML chronic phase	CCyR, MMR	Moderate
Kantarjian et al[32]	US	RCT	NA	564	CML chronic phase	CCyR, MMR	Moderate
Kantarjian et al[35]	US	RCT	NA	564	CML chronic phase	CCyR, MMR	Moderate
Larson et al[33]	US	RCT	NA	564	CML chronic phase	CCyR, MMR	Moderate
Nakamae et al[36]	Japan	RCT	52	49	CML chronic phase	CCyR, MMR	Moderate
Nakamae et al[37]	Japan	RCT	52	48	CML chronic phase	CCyR, MMR	Moderate
Nakamae et al[40]	Japan	RCT	52	564	CML chronic phase	CCyR, MMR	Moderate
Saglio et al[34]	UK	RCT	47	564	CML chronic phase	CCyR, MMR	Moderate
Wang et al[30]	China	RCT	41	267	CML chronic phase	CCyR, MMR	Moderate
Yin et al[39]	China	RCT	NA	101	CML chronic phase	CCyR, MMR	Moderate
Zhang et al[38]	China	RCT	NA	80	CML chronic phase	CCyR, MMR	High
Dasatinib vs nilotinib							
Adel et al[27]	Qatar	Retrospective	NA	58	CML chronic phase	CCyR, MMR	High
Iriyama et al[28]	Japan	Retrospective	NA	120	CML chronic phase	MMR, DMR	High
Jain et al[24]	US	RCT	49	196	CML chronic phase	CCyR, MMR	Moderate
Suh et al[29]	South Korea	Retrospective	54	105	CML chronic phase	CCyR, MMR	Moderate
Takahashi et al[26]	US	RCT	49	174	CML chronic phase	CCyR, MMR	Moderate

UK: United Kingdom, US: United States, RCT: Randomized controlled trials, NA: Not available, CML: Chronic myeloid leukemia. CCyR: Complete cytogenetic response, MMR: Major molecular response

dasatinib and imatinib. The newer TKIs were found to be more potent than imatinib, with dasatinib and nilotinib showing equivalent MMR rates (Signorovitch, 2011).[8,43–45] However, these studies had several limitations, including small sample sizes and the nature of indirect comparisons. In contrast, our study had a larger sample size and performed direct comparisons, providing a clearer understanding of the associations than indirect comparisons. Therefore, our study likely offers higher-quality evidence compared to previous studies.

The precise mechanisms underlying our findings remain incompletely understood. However, several plausible explanations can be proposed. Dasatinib targets the active state of BCR-ABL, while imatinib and nilotinib target the inactive state. This allows dasatinib to effectively inhibit BCR-ABL even in the presence of mutations that confer resistance to imatinib. Although nilotinib also binds to the inactive form of BCR-ABL, it demonstrates a superior topographical fit in the ABL kinase pocket compared to imatinib, enhancing its potency against a range of resistant mutations.[10] Thus, the

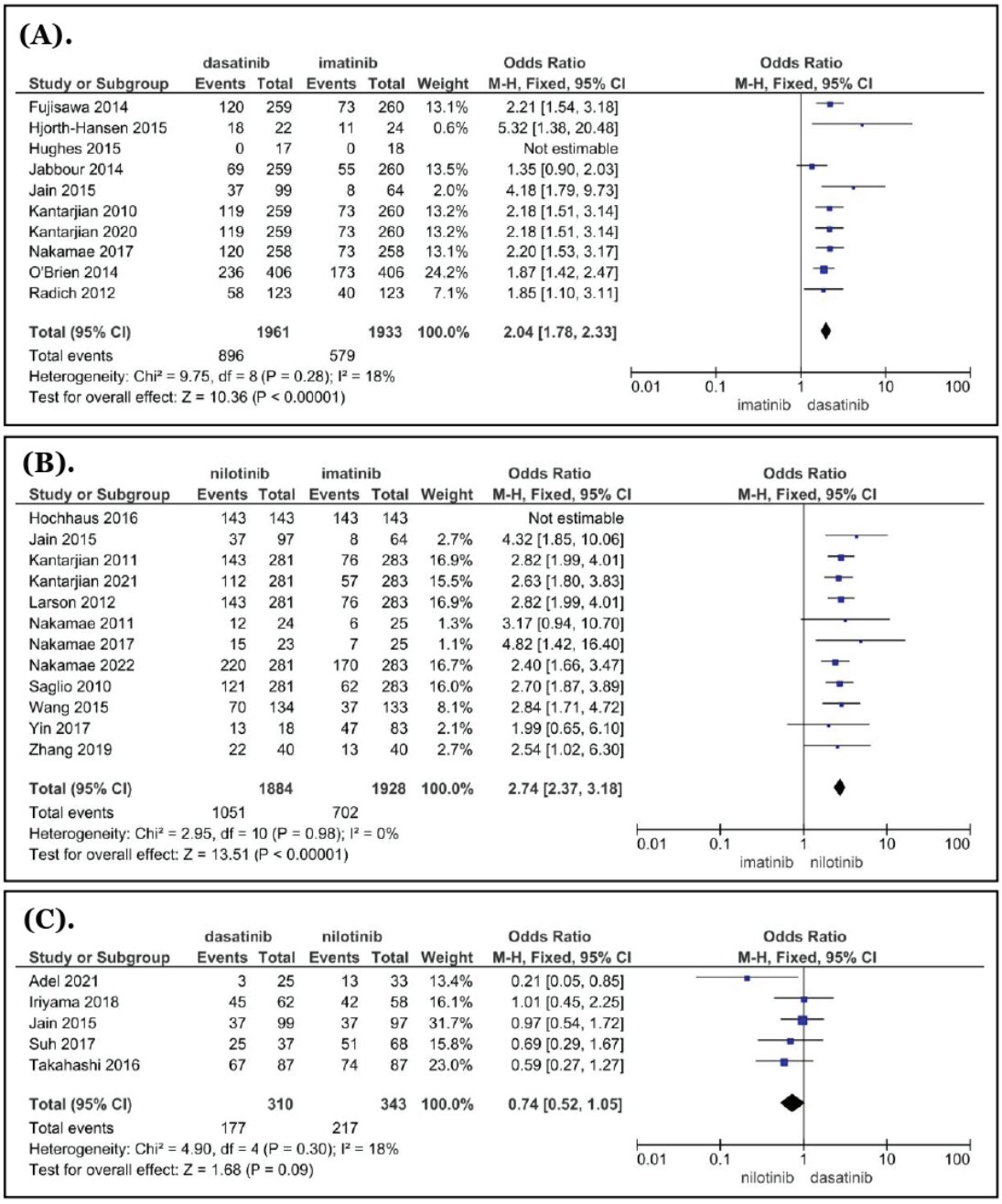

Figure 2. The impact of imatinib, dasatinib, and nilotinib on the major molecular responses in newly diagnosed chronic myeloid leukemia patients. **(A)** Dasatinib vs imatinib (OR: 2.03; 95% CI: 1.77, 2.32; p Egger: 0.3234; p heterogeneity: 0.3550; p<0.0001). **(B)** Nilotinib vs imatinib (OR: 2.75; 95% CI: 2.41, 3.18; p Egger: 0.2376; p heterogeneity: 0.9500; p<0.0001). **(C)** Dasatinib vs nilotinib (OR: 0.74; 95% CI: 0.52, 1.05; p Egger: 0.0643; p heterogeneity: 0.3000; p: 0.0900).

differences in the mechanisms of action of dasatinib, nilotinib, and imatinib are attributable to their distinct binding conformations and varying potencies. Dasatinib's binding to the active conformation and its higher potency contribute to its effectiveness against resistant mutations, whereas nilotinib's improved fit in the ABL kinase pocket increases its efficacy against resistant mutations relative to imatinib.[9,10]

This study had several important clinical implications. Firstly, it represented the first investigation to directly compare the achievement of MMR12 among dasatinib, imatinib, and nilotinib in the management of chronic phase CML. This comparison provided novel insights into the relative efficacy of these TKIs in achieving MMR12. Secondly, the findings offered valuable information regarding the po-

Table 2. The summary of analysis of the impact of imatinib, dasatinib, and nilotinib on the major molecular responses 12 in newly diagnosed chronic myeloid leukemia patients.

Covariates	MMR12/total (n[%])	Model	NS	OR	95% CI	P Egger	P Het	p
Dasatinib versus imatinib	1,475/3,894	Fixed	10	2.03	1.77–2.32	0.3234	0.3550	<0.0001
Nilotinib versus imatinib	1,686/4,090	Fixed	12	2.75	2.41–3.18	0.2376	0.9500	<0.0001
Dasatinib versus nilotinib	394/654	Fixed	5	0.74	0.52–1.05	0.0643	0.3000	0.0900

OR: Odds ratio, CI: Confidence interval, NS: Number of studies, p Het: p heterogeneity, MMR: Major molecular response

tential effectiveness of dasatinib, nilotinib, and imatinib, contributing to our understanding of their capabilities in inducing MMR12 in patients with chronic phase CML. Thirdly, the results have the potential to inform the development of clinical guidelines and management strategies for chronic phase CML, by providing evidence-based data on the relative performance of these treatments. Lastly, the study established a foundation for future research aimed at exploring the long-term effectiveness of dasatinib, nilotinib, and imatinib in achieving and maintaining MMR, thereby advancing our knowledge of their efficacy over extended treatment periods.

This study had several notable limitations. Firstly, it did not account for possible confounding variables such as patient age, history of prior therapies, and duration of the treatment regimen, all of which could have influenced the study's results. Consequently, these unexamined variables might have impacted the observed outcomes and warrant consideration in future research. Secondly, the study was constrained by a limited sample size, which suggests that the results need to be interpreted carefully and may not fully represent the broader population. Thirdly, the study population was not evenly distributed across different geographic regions, which implies that the generalizability of the results to various global populations is limited. Fourthly, due to constraints in available data, the study focused exclusively on the achievement of MMR12, without assessing other potential indicators of therapy efficacy. Future studies that examine a broader range of therapy responses would be beneficial to provide a more comprehensive evaluation. Finally, this study assessed treatment success solely in terms of MMR12 and did not consider cytogenetic responses, which are also important measures of treatment effectiveness.

In conclusion, our findings demonstrated that dasatinib and imatinib both exhibited superior efficacy in achieving MMR12 compared to imatinib in the treatment of chronic phase CML. These results contribute valuable knowledge regarding the roles of dasatinib, nilotinib, and imatinib in managing chronic phase CML. The findings from this study may serve as a foundation for developing future clinical guidelines and management strategies for CML, potentially improving treatment protocols and patient outcomes in the future.

ΠΕΡΙΛΗΨΗ

Μείζονες μοριακές απαντήσεις στη νεοδιαγνωσθείσα χρόνια μυελογενή λευχαιμία: Μια μετα-ανάλυση της πορείας μετά από θεραπεία ενός έτους με δασατινίμπη, ιματινίμπη και νιλοτινίμπη

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ΣΚΟΠΟΣ Η αξιολόγηση της αποτελεσματικότητας της ιματινίμπης (imatinib), της δασατινίμπης (dasatinib) και της νιλοτινίμπης (nilotinib) στην επίτευξη μείζονος μοριακής ανταπόκρισης στους 12 μήνες (MMR12) ως θεραπείες πρώτης γραμμής για τη χρόνια φάση της χρόνιας μυελογενούς λευχαιμίας (ΧΜΛ). **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Διεξήχθη μετα-ανάλυση χρησιμοποιώντας δεδομένα που εξήχθησαν από τα PubMed, Embase και Scopus, τα οποία καλύπτουν την περίοδο από τον Μάιο έως τον Ιούνιο του 2024. Οι πληροφορίες για τη MMR12 από κάθε μελέτη συγκεντρώθηκαν για την εκτίμηση των μεγεθών των επιπτώσεων, εφαρμόζοντας τη μέθοδο Mantel-Haenszel. Η στατιστική ανάλυση πραγματοποιήθηκε με το Review Manager 5.1. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Η ανάλυση περιλάμβανε συνολικά 27 άρθρα. Τα ευρήματά

μας έδειξαν ότι η δασατινίμπη επέδειξε υψηλότερη αποτελεσματικότητα στην επίτευξη MMR12 σε σύγκριση με την ιματινίμπη (σχετικός λόγος [OR]: 2,03, 95% διάστημα εμπιστοσύνης [ΔΕ]: 1,77–2,32, p<0,0001). Επί πλέον, η νιλοτινίμπη βρέθηκε να είναι περισσότερο αποτελεσματική από την ιματινίμπη για τη θεραπεία της χρόνιας φάσης της ΧΜΛ (OR: 2,75, 95% ΔΕ: 2,41–3,18, p<0,0001). Τέλος, η δασατινίμπη και η νιλοτινίμπη είχαν παρόμοια αποτελέσματα στη θεραπεία ασθενών με ΧΜΛ (OR: 0,74, 95% ΔΕ: 0,52–1,05, p=0,0900). **ΣΥΜΠΕΡΑΣΜΑΤΑ** Η δασατινίμπη και η νιλοτινίμπη εμφανίζουν την περισσότερο υποσχόμενη αποτελεσματικότητα ως θεραπείες πρώτης γραμμής για τη χρόνια φάση της ΧΜΛ με βάση την επίτευξη της MMR12.

Λέξεις ευρετηρίου: Δασατινίμπη, Ιματινίμπη, Κύρια μοριακή απόκριση στους 12 μήνες, Νιλοτινίμπη, Χρόνια μυελογενής λευχαιμία

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