REVIEW

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CHRONIC MYELOID LEUKAEMIA REMISSION STABILITY AFTER TYROSINE - KINASE INHIBITORS THERAPY CESSATION: A REVIEW OF LITERATURE

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Summary

Introduction: Chronic myeloid leukaemia (CML) is a specific malignant disease as it can be managed by a long-term oral tyrosine-kinase inhibitors (TKIs) treatment. Routine practise in the management of CML includes continuation of TKIs therapy even after the patient achieves remision. Several trials have demonstrated that TKIs discontinuation is feasible in clinical practice. The aim of this paper is to assess relevant scientific evidence on CML remission stability after TKIs therapy cessation.

Methods: For systematic search, we used the MEDLINE/PubMed (National Library of medicine) Cochrane Central Register of Controlled Trials and Embase database. The last search update was on 31st December 2020. The search included observational cohort studies and randomized condrolled trials that evaluated treatment-free remission after TKIs therapy cessation.

Results: A literature review provides data that patients with CML mostly achieve clinically feasible treatment free remission (TFR). The eleven studies incuded 1249 patients. After an average follow-up of 37 months (16 to 103), overall estimated TFR was 51% (35% to 64%).

Conclusion: Evidence from reviewed studies indicated that discontinuation of TKIs is feasible and safe in the clinical practice.

KEYWORDS: *chronic myeloid leukaemia, tyrosine-kinase inhibitors, discontinuation*

INTRODUCTION

Chronic myeloid leukemia (CML) is a disease characterized by malignant transformation of a pluripotent hematopoietic stem cell. Mostly occurs in middle and old age, making up about 20% of all forms of leukemia(1). CML is specific for the cytogenetic change of the Philadelphia chromosome and the formation of a fusion gene with the production of the BCR-ABL protein whose excessive tyrosine kinase activity stimulates increased cell production(2).

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The most important finding in the treatment of CML was a tyrosine kinase inhibitor (TKI) that successfully stops the BCR-ABL protein in causing inhibition of its enzymatic activity(2). In the first line of modern therapy of CML, is one of the three tyrosine kinase inhibitors (TKIs): imatinib (IM), dasatinib or nilotinib. Orally taken IM is the gold standard for first therapy in patients with recently diagnosed CML. After the introduction of IM in the treatment of CML, the mortality rate, after the first year of being diagnosed, dropped to about 2%. In the eight-year period after diagnosis, survival is more than 80%. If remission occurs within a year, these patients are less likely to die from leukemia(3).

To summarise, TKIs form the fundamental perspective of modern CML treatment, with more than 80% of patients achieving a complete cytogenetic response and 40% complete molecular remission(4). However, imatinib treatment, as well as recent generations of TKIs, is expensive, can have a toxic effect, and requires strong patients' adherence. Therefore, the safety of discontinuation of TKIs therapy after achieving remission has been intensively under research. The aim of this paper is to review the current information based on the available published data on the safety of discontinuation of TKIs after achieving remission in CML and discuss current suggestions on how to move treatment-free remission (TFR) into clinical practice.

METHODS

Search strategy

The research question we asked when searching the literature was: is remission maintained in patients treated for CML who have achieved deep molecular remission with TKIs even after their TKIs has been discontinued? We systematically searched MEDLINE, Cochrane Central Register of Controlled Trials and Embase for all studies published in English between January 2010 and 2021 using relevant keywords and controlled vocabulary that included: chronic myeloid leukemia, tyrosine kinase inhibitor, discontinuation. Additional studies were identified by manual search of references of original studies.

Study inclusion and outcomes

The population of interest for literature review are adult patients treated for CML with TKIs, imatinib, nilotinib or dasatinib, whose therapy was discontinued after achieving deep molecular remission, which is also the intervention of the study group. We included observational cohort studies and randomized condrolled trials that evaluated TFR after achieving deep molecular remission. Articles excluded from the search were those older than 11 years, as well as those with a sample of less than 15 respondents or if the paper does not include research on adults.

Data extraction and quality assessment

Study selection and data extraction were conducted independently by two investigators. All disagreements or differences in the data extraction between the two authors were harmonized by consensus after the source data had been rechecked. TFR (treatment-free remission) has been evaluated as a criterion in patients with CML who had stopped TKI after prolonged complete molecular response. Studies were included if the available information in the abstract made it clear that the article was eligible. Full texts were read independently by reviews.

RESULTS

The database's search yielded 93 articles. Based on the title and abstract analysis and review of potentially relevant studies, 11 studies were included in the final analysis (figure 1). All the studies included patients with Philadelphia positive (Ph+) CML in chronic phase who had discontinued TKI treatment in deep molecular response and with a follow-up after discontinuation longer than 1 year. Also, every study included the TFR rate as the primary endpoint, after at least one year from TKI treatment discontinuation. The studies incuded 1249 patients. After an average follow-up of 37 months (16 to 103) overall estimated treatment free remission was 51% (range from 35% to 64%). Results are presented in table 1.

One of the first Stop Imatinib Trial studies was performed to demonstrate the efficacy or ineffectiveness of discontinuation of TKIs therapy in patients in remission from CML. Patients treated with imatinib for more than two years in complete molecular remission were included. Relapse of the disease occurred in 61% of patients most often within six months of discontinuation of therapy. Other patients maintained complete molecular remission for more than 12 months. All patients who restarted therapy due to disease relapse responded favorably to re-introduction of imatinib. An update to this study estimated the likelihood of relapse at 10% for those patients who manage to maintain remission for the first six months(16,17).

A national study in Japan examined 50 patients in remission who discontinued imatinib at 6 months and the remission rate after discontinuation of imatinib was estimated at 47%(15).

A prospective clinical study called Twister included 40 adult patients who discontinued imatinib therapy for at least 36 months after at least 2 years of stable molecular remission. The median

follow-up was 42 months with a range of a minimum of 15 months to a maximum of 72 months. After 24 months, the assessment of stable remission without treatment was 47.1%. The majority of relapses, 15 of 22 (68%), occurred within 6 months (median 3 months) of discontinuation of therapy. The remaining 7 relapses were reported between 6 and 27 weeks (median 14.5 weeks) after discontinuation of imatinib. After 27 weeks of follow-up, the remaining patients maintained stable remission at 42.7%(12).

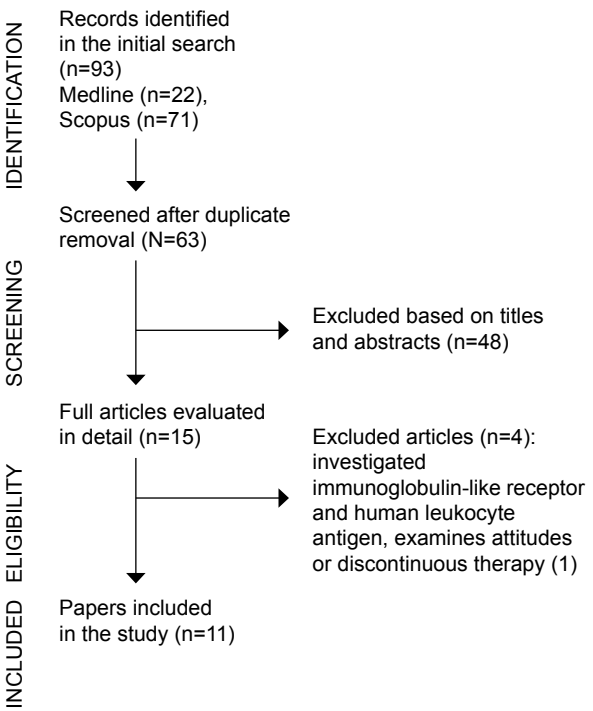

Fig. 1. Studies selection progress

A large multicenter observational study in a sample of 80 patients in molecular relapse, whose imatinib therapy was discontinued, aimed to investigate the loss of the deep molecular response as a criterion for continuing therapy. In the patients enrolled in the study, the median from the start of imatinib therapy to cessation was 79 months, and the median duration of complete molecular remission before cessation of imatinib was 41 months, with a median follow-up of 31 months. Out of a total of 80 patients, 29 lost profound molecular remission ranging from 2 to 17 months after discontinuation of therapy. The cumulative incidence of remission loss was estimated at 35% at 12 months and 36% at 24 months. Remission was maintained in 64% of patients within 12 and 24 months and 61% within 16 months(13).

A French RE-STIM observational multicenter study included patients in a repeat procedure to discontinue TKI therapy after the first failed attempt to maintain remission without therapy. The median follow-up was 38 months and included 70 patients. 45 (64%) relapsed on average 5.3 months after discontinuation of therapy. The majority of relapses (54%) occurred within the first year after discontinuation of therapy. All patients resumed TKI therapy. This study is the first to show that a second attempt to discontinue a TKI is also safe and that the first failed attempt does not preclude a second successful one(8).

Table 1.

Key characteristics of included studies

Author (reference)	Patients (N)	Mean age (years)	Male (%)	Months after discontinuation	The TFR rate
Fava et al. (5)	293	49	55%	34	62% (95% CI 56;68)
Hernández-B et al. (6)	236	61	48%	48	64% (95% CI 55;72)
Kumagai et al. (7)	54	56	59%	16	63% (95% CI 48;74)
Legros et al. (8)	70	51	NA	36	35% (95% CI 24;49)
Mahon et al. (9)	126	56	44%	24	53% (95% CI 44;62)
Nagafuji et al. (10)	149	55	59%	36	61% (95% CI 52;70)
Rea et al. (11)	60	60	37%	48	54% (95% CI 40;67)
Ross et al. (12)	40	60	48%	103	45% (95% CI 32;63)
Rousselot et al. (13)	80	55	52%	36	61% (95% CI 51;73)
Shen et al. (14)	45	36	51%	24	40% (95% CI 29;52)
Takahashi et al. (15)	96	55.5	62%	24	63% (95% CI 51;73)

DISCUSSION

The most important discovery in the treatment of CML was a TKI, which significantly reduces the mortality rate of patients. Recently, the safety of discontinuation of TKI therapy after achieving deep molecular remission for at least two years has been intensively investigated in order to improve the quality of life of patients and reduce treatment costs. By reviewing published studies, we found that after stopping the first TKI treatment, between 35% and 64% of all patients remained in stable remission for months after discontinuation of therapy. Also, patients who had relapse of the disease after discontinuation of therapy retained susceptibility to TKI, suggesting that discontinuation does not lead to resistance and does not cause further safety concerns(5–15).

Systematic review or meta-analysis that evaluated the safety of TKIs discontinuation in CML patients are rarity. The first systematic review of the literature with meta-analysis was published in 2017. The purpose of this study was different from our review of the TFR after discontinuation of therapy because the authors focused on disease relapse. The mean relapse of CML after discontinuation of therapy was 51%. All patients survived two years of follow-up, and the study suggests that discontinuation of therapy does not increase disease progression and risk of death(18).

In their 2018 review, Breccia and Foà also dealt with the discontinuation of TKI in chronic phase chronic myeloid leukemia (CP-CML) and concluded that discontinuation is feasible and safe if performed in patients with a long-lasting deep molecular response(19).

The most recent systematic review and meta-analysis included 10 trials with 1,601 patients. Authors concluded that TFR as an extension of an approach to optimize management of CML is clinically feasible in approximately 59% of patients with sufficient TKI response. In the remaining 41% of patients with molecular relapse, discontinuing TKIs had no negative impact on clinical outcomes(20).

CONCLUSION

A literature review provides data that patients with CML with sufficient TKIs response for at least two years mostly achieve clinically feasible TFR. In discontinuation therapy studies, it is crucial to determine predictive discontinuation factors, disease prognosis, and risk factors for relapse. Discontinuation of therapy is recommended only in clinical circumstances, which include monitoring of the molecular response and careful selection of patients based on criteria.

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Sažetak

STABILNOST REMISIJE KRONIČNE MIJELOIČNE LEUKEMIJE NAKON PREKIDA TERAPIJE INHIBITORIMA TIROZIN KINAZE: PREGLED LITERATURE

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Uvod: Kronična mijeloična leukemija (KML) specifična je maligna bolest s obzirom da se liječenje provodi oralnom primjenom inhibitora tirozin-kinaze (TKI). Rutinska praksa podrazumijeva korištenje TKI i nakon što bolesnik postigne potpunu remisiju bolesti, no recentna istraživanja navode uspjeh u kontroliranju bolesti I nakon što se prekine terapija TKI. Cilj ovog rada je sustavnim pregledom literature prikupiti relevantne znanstvene činjenice o uspješnosti održavanja remisije KML nakon prekida terapije TKI.

Metode: Za sustavno pretraživanje literature kosistili smo MEDLINE, Cochrane i Embase baze podataka. Posljednje ažuriranje pretraživanja bilo je 31. prosinca 2020. Pretraga je uključivala randomizirana klinička ispitivanja i opservacijske kohortne studije koje su procjenjivale uspješnosti održavanja remisije KML nakon prekida terapije TKI.

Rezultati: Pregled literature daje podatke da bolesnici s KML-om uglavnom postižu klinički izvedivu remisiju nakon prekidanja liječenja. Jedanaest studija obuhvatilo je 1249 pacijenata. Nakon prosječnog praćenja od 37 mjeseci (16 do 103), ukupna procijenjena remisije bila je kod 51% bolesnika (35% do 64%).

Zaključak: Dokazi iz literature potvrđuju da je kod određenog dijela pacijenata prekid terapije siguran. Preporučljivo je prekidanje terapije samo u kliničkim uvjetima uz praćenje molekularnog odgovora.

KLJUČNE RIJEČI: *kronična mijeloična leukemija, inhibitori tirozin kinaze, prekid liječenja*