Int J Clin Exp Med 2019;12(12):13337-13347
www.ijcem.com /ISSN:1940-5901/IJCEM0098656

Original Article

The efficacy of TKI in patients with different BCR/ABL transcript types of chronic myeloid leukemia: a systematic review and meta-analysis

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Received June 19, 2019; Accepted November 6, 2019; Epub December 15, 2019; Published December 30, 2019

Abstract: There was controversy about the efficacy of tyrosine kinase inhibitor (TKI) in the treatment of different transcripts. Some reported that the e14a2 transcript performing TKI treatment showed much better efficacy, however, other studies did not come to consistent results. In order to estimate the efficacy of TKI in patients with different BCR/ABL transcript types of chronic myeloid leukemia (CML), we searched published articles or internationally accepted abstracts from PubMed, Embase, Medline, Cochrane library, China Knowledge Network (CNKI), Chinese Biomedical Abstracts Database (CBM), Wanfang Database and Chinese Veterinary Science Database (VIP) before January 2019. Data such as stage, the BCR/ABL transcript type, use of TKI drugs, the rate of major molecular response (MMR), the rate of complete cytogenetic response (CCyR) and the rate of 5-year overall survival (OS) were extracted from each included study. Of 2768 citations, 16 clinical trials were selected and included in the review. Results revealed that the 6-month MMR rate and long-term MMR rate in the e13a2 group were much lower than that in the e14a2 group after TKI treatment. The 5-year OS rate in the e13a2 group was lower than that in the e14a2 group. In addition, the 12-month CCyR rate in the e13a2 group was also lower than that in the e14a2 group. However, the 6-month CCyR rate had no significant difference between e13a2 group and e14a2 group. Therefore, we believed that the 6-month MMR rate, the long-term MMR rate, the 5-year OS rate and the 12-month CCyR rate were correlated with the BCR/ABL transcript in patients with CML after TKI treatment. The e14a2 transcript performing TKI treatment showed much better efficacy.

Keywords: Chronic myeloid leukemia, TKI, BCR/ABL, meta-analysis

Introduction

Chronic myeloid leukemia (CML) was generally characterized by the Philadelphia chromosome that was the result of a reciprocal translocation between the ABL gene locating in the chromosome 9 and the BCR gene locating in chromosome 22. The most common breakpoints in the BCR gene and the ABL gene were exons e13, e14 and exons a1, a2 correspondingly. The e13a2 and the e14a2 were the most common transcript types generated by different BCR/ABL transcript types [1]. This reciprocal translocation resulted in the BCR/ABL fusion gene that encoded the protein product with tyrosine kinase activity. The e13a2 and e14a2 BCR/ABL transcript differed in length by 75 bp, which indicated that the two BCR/ABL transcripts were different in structure.

Both the e13a2 and the e14a2 transcript encoded the P210 protein, however, the difference of 2 transcripts might lead to different clinical characteristics in gene structure. Furthermore, the platelet level of patients with e14a2 transcript was higher than that e13a2 transcript. The leucocyte level of patients with e14a2 transcript was lower than that e13a2 transcript. It had also been reported that patients with the e13a2 transcript are more commonly male [2]. Patients with e13a2 transcript had a higher risk of transition to acute phase during the treatment with Tyrosine kinase inhibitor (TKI) [3, 4]. All of this indicated that the

function and mechanism of e14a2 transcript and e13a2 transcript might be different in cancer development.

The emergence of TKI has significantly improved the prognosis of CML patients [3]. The overall survival (OS) of CML patients was close to normal during TKI treatment, which benefited from cytogenetics and molecular monitoring. Cytogenetics and molecular monitoring also can guide the TKI treatment and evaluate the efficacy of TKI. However, the expensive drug and the side effects of TKI had seriously affected patients' quality of life [5]. Some reported that the OS of CML patients might be shorted because of the occurrence of secondary tumour and cardiovascular events associating with long-term TKI treatment [3, 6]. Meanwhile, studies also showed that the e14a2 transcript and e13a2 transcript presented different therapeutic effects during TKI treatment. Therefore, we believed that the different transcript types of CML patients had the necessity for further research.

There was controversy about the efficacy of TKI in the treatment of 2 different transcripts. Some studies reported that patients with e14a2 BCR/ABL transcript could achieve earlier major molecular response (MMR) than patients with e13a2 transcript [7, 8]. However, Ali et al [9] reported that there was no statistically significant difference in MMR between the e14a2 transcript and the e13a2 transcript. Studies reported the complete cytogenetic response (CCyR) and 5-year OS rate in patients with different BCR/ABL transcript types during TKI treatment, however, their results were not consistent [10, 11]. Pagnano et al [8] showed that the CCyR in patients with e14a2 transcript was higher than that in patients with e13a2 transcript during TKI treatment. However, Jain et al [7] did not find a difference in the CCyR between the 2 transcripts. In addition, there was also no consistent result regarding the rate of 5-year OS rate between the e14a2 transcript and the e13a2 transcript.

In the present study, given the inconsistent results regarding efficacy of the 2 transcripts during TKI treatment, we present the meta-analysis to evaluate the efficacy of TKI treatment in patients with different BCR/ABL transcript types. Meanwhile, we also planned to select drug-resistant BCR/ABL transcript and provide a new basis for further improving the precise therapy of TKI.

Materials and methods

Literature search strategy

Published articles or internationally accepted abstracts were searched from PubMed, Embase, Medline, Cochrane library, China Knowledge Network (CNKI), Chinese Biomedical Abstracts Database (CBM), Wanfang Database and Chinese Veterinary Science Database (VIP) before January 2019. The key words used for searching articles were as follows: e13a2, e14a2, chronic myeloid leukemia, BCR/ABL, imatinib and tyrosine kinase inhibitor.

Inclusive and exclusive criteria

Inclusive criteria: (1) patients with CML diagnosed by molecular biology, bone marrow cytology and cytogenetics; (2) results involved the efficacy of different BCR/ABL transcripts from randomized controlled trial or cohort study; (3) TKI was the main treatment in patients with CML; (4) all studies included the CCyR rate, the MMR rate and the OS rate. Exclusive criteria: (1) studies did not include the control group; (2) studies included insufficient data; (3) duplicated publications; (4) review, letter, case report and comment.

Study selection and data extraction

Two researchers completed the screening of articles independently according to the inclusive and exclusive criteria. If the two researchers present disputes about the included literature, a third researcher coordinated to solve it. The main information included the first author, year of publication, country, the staging of disease, the sample size, BCR/ABL transcripts, the 6-month MMR rate, the long-term MMR rate, the 6-month CCyR rate, the 12-month CCyR rate, the 5-year OS rate and so on.

Quality assessment

The quality of cohort studies was independently assessed by two researchers according to the Newcastle-Ottwa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

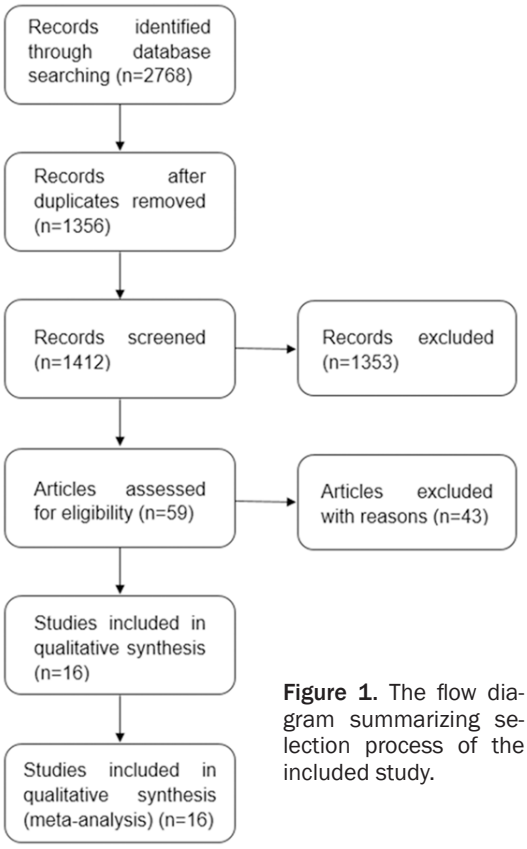

Figure 1. The flow diagram summarizing selection process of the included study.

Statistical analysis

Review Manager version 5.3 (The Cochrane Collaboration, Software Update, Oxford) was used to perform the meta-analysis. The outcome indicators of this study were MMR rate, CCyR rate and 5-year rate. The included research was cohort studies, variables were dichotomous variables. Heterogeneity across studies was evaluated by Cochran's Q-statistic test (P<0.1 was considered as statistically significant heterogeneity). Dichotomous variables were tested by relative Ratio (RR) with a 95% confidence interval (95% CI). Between-study heterogeneity was assessed by χ^2 and I^2. Data that were not significantly heterogeneous (P> 0.1) were performed using the fixed effects model, and heterogeneous data (P<0.1) were analysed using the random-effects model. We performed a subgroup analysis to explore the reason of heterogeneity on the 6-month CCyR rate and 12-month CCyR rate. Our study was divided into two subgroups (one generation group and two generation group) according to the generation of TKI to explore whether the generation of TKI affected the efficacy. To estimate the stability of each result in our study, sensitivity analysis was performed by conversing effect model. A value of $P \leq 0.05$ was considered statistically significant.

Results

Characteristics of included studies

Of 2768 citations, 16 clinical trials were selected and included in the meta-analysis. A flow diagram summarizing selection process of the included study could be found in **Figure 1**. Research collection and screening was completed on January 2019. All of the 16 studies involved the efficacy of TKI treatment in patients with different BCR/ABL transcripts. All studies included e13a2 transcript and e14a2 transcript. **Table 1** presented the characteristics of included studies.

Evaluation for qualities of studies

The standards of Newcastle-Ottawa Scale (NOS) were used to assess the included studies. For the cohort studies, 1 study scored 9 points, 4 studies scored 8 points, 7 studies scored 7 points and 4 studies scored 6 points (**Table 1**).

The MMR rate of e13a2 transcript versus e14a2 transcript

The 6-month MMR rate was reported in 5 articles with 862 participants [2, 7-10]. There was no statistical heterogeneity among this literature (X^2=7.52; P=0.11; I^2=47%). Therefore, the fixed effects model was used to analyse the results. The result of meta-analysis indicated that the 6-month MMR rate in the e13a2 transcript group was lower than that in the e14a2 transcript group (RR=0.69; 95% CI: 0.59-0.80; P<0.001) (**Figure 2A**).

Eight articles with 1130 participants reported the long-term MMR rate (the time of patients achieving MMR more than 12 months) during TKI treatment [2, 7-13]. There was also no statistical heterogeneity among the literature (X^2=10.52; P=0.16; I^2=33%). Therefore, the fixed effects model was used to analyze. There were significant difference in the long-term MMR rate between the e13a2 transcript group

Table 1. The characteristics of included studies

Author/year	NOS score	Country	Age	Treatment	Dose (mg/d)	Observation indexes
Castagnetti/2017 [18]	7	Italy	>18	a*	400-800	③ ④
Pfirrmann/2017 [15]	8	Europe	>18	a*	400-800	⑤
Pagnano/2017 [8]	8	Brazil	18-87	a*	400-800	① ③ ④
Lucas/2009 [20]	7	Britain	>16	a*	400	④
Polampalli/2008 [10]	7	India	NR	a*	NR	①
Rostami/2017 [21]	9	Saba	17-81	a*	400-800	④
Lin/2016 [2]	8	Canada	18-91	a*	400	①
Lee/2018 [14]	7	Korea	14-77	a*	NR	⑤
Azad/2018 [17]	8	India	7-75	a*	NR	②
Castagnetti/2016 [11]	6	NR	NR	b*	600-800	③
Genthon/2017 [19]	7	NR	19-85	b*	600	④
Su/2017 [16]	7	NR	>18	b*	NR	⑤
Ali/2017 [9]	6	America	20-87	c*	NR	①
Elbjeirami/2016 [12]	6	Saudi	16-76	a*	NR	②
Deb/2014 [13]	6	NR	NR	a*	NR	③
Jain/2016 [7]	7	America	37-58	c*	NR	① ② ③

Abbreviations: outcome indicator: ①, the 6-month MMR rate; ②, the long-term MMR rate; ③, the 6-month CCyR rate; ④, the 12-month CCyR rate; ⑤, the 5-year rate of overall survival (OS); NR, not reported; NOS, Newcastle-Ottawa Scale; a*, one generation of TKI; b*, two generation of TKI; c*, TKI (not distinguish generation).

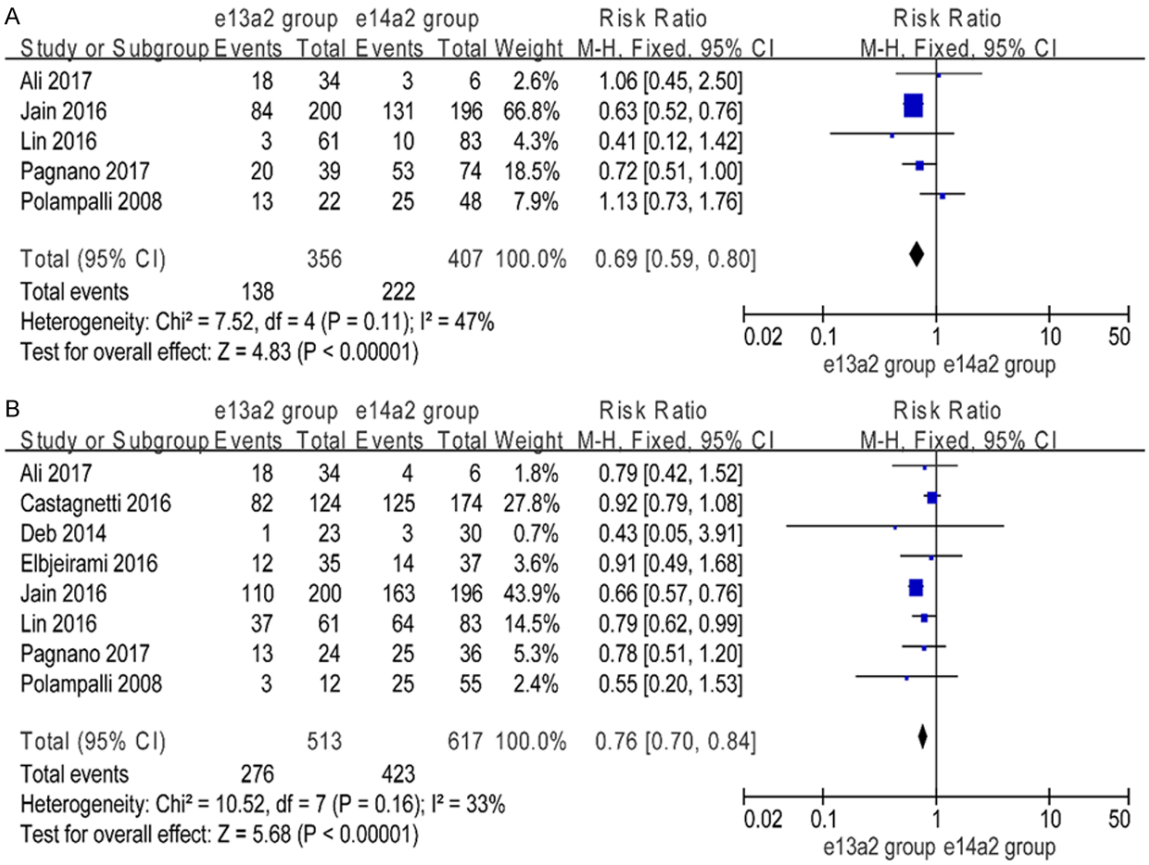

Figure 2. A. The forest plot of the 6-month MMR rate between the e13a2 and e14a2 transcript; B. The forest plot of the long-term MMR rate between the e13a2 and e14a2 transcript.

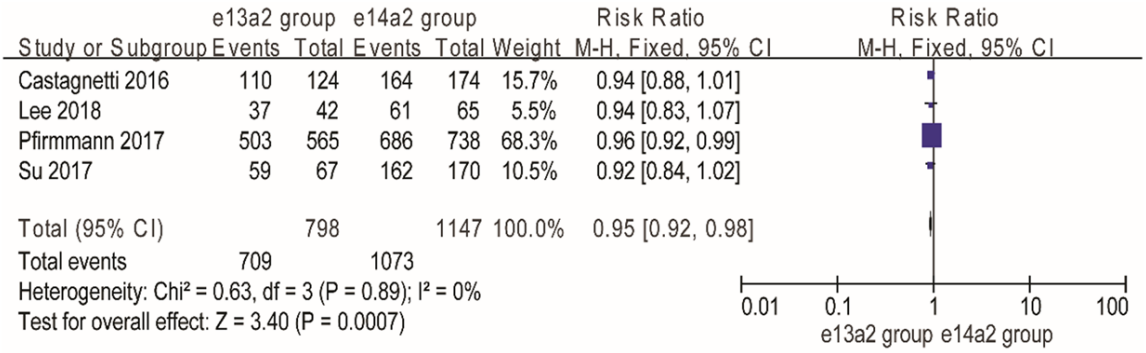

Figure 3. The forest plot of the 5-year OS rate between the e13a2 and e14a2 transcript.

and the e14a2 transcript group, and the long-term MMR rate in the e14a2 transcript group was higher than that in the e13a2 transcript group (RR=0.76; 95% CI: 0.70-0.84; P<0.001) (**Figure 2B**).

The 5-year OS rate of e13a2 transcript versus e14a2 transcript

Four articles with 1945 participants reported the 5-year OS rate during TKI treatment [11, 14-16], and no evidence of heterogeneity was found (X^2=0.63; P=0.89; I^2=0%). Therefore, we used the fixed effects model for analysis. Result of meta-analysis on the 5-year OS rate showed a significant increase in the e14a2 transcript group. The 5-year OS rate in the e13a2 transcript group was lower than that in the e14a2 transcript group (RR=0.95; 95% CI: 0.92-0.98; P=0.0007) (**Figure 3**).

The CCyR rate of e13a2 transcript versus e14a2 transcript

Five articles with 1108 participants had evaluated the 6-month CCyR rate, and heterogeneity was significant among the literature (X^2=14.96; P=0.005; I^2=73%). However, there was no significant difference in the 6-month CCyR rate between the e13a2 transcript and the e14a2 transcript group (RR=0.99; 95% CI: 0.86-1.14; P=0.93) [7, 8, 17-19]. Therefore, the random-effect model was used to analyze (**Figure 4A**).

Six articles with 899 participants had evaluated the 12-month CCyR rate, and there was statistically significant heterogeneous among the literature (X^2=17.04; P=0.004; I^2=71%) [8, 16-18, 20, 21]. The random-effect model was used to compare the 12-month CCyR rate in the two groups. Result showed a significant increase in the e14a2 transcript group on the 12-month CCyR rate. The 12-month CCyR rate in the e13a2 transcript group was lower than that in the e14a2 transcript group (RR=0.81; 95% CI: 0.65-1.00; P=0.05) (**Figure 4B**).

Subgroup analysis

We performed a subgroup analysis to explore the reason of heterogeneity on the 6-month CCyR rate. Our study was divided into two subgroups (one generation group and two generation group) according to the generation of TKI to explore whether the generation of TKI affected the efficacy, however, our result revealed that there was no statistical significance in subgroup analysis (RR=0.93, 95% CI: 0.71-1.22, P=0.61; RR=0.94, 95% CI: 0.79-1.11, P=0.17) (**Figure 5**). Therefore, we believed that the generation of TKI might not be the reason of heterogeneity on 6-month CCyR rate.

In addition, we also performed a subgroup analysis to explore the reason of heterogeneity on the 12-month rate of CCyR. The result revealed that there was no statistical significance in subgroup analysis of generation of TKI (RR=0.81, 95% CI: 0.63-1.05, P=0.11; RR=0.74, 95% CI: 0.57-0.97, P=0.03) (**Figure 6**). We believed that the generation of TKI might be the reason of heterogeneity on 12-month CCyR rate.

Sensitivity analysis and publication bias

We performed the sensitivity analysis of each result by conversing effect model. The result of each group was the same as the above results. The result of sensitivity analysis showed that

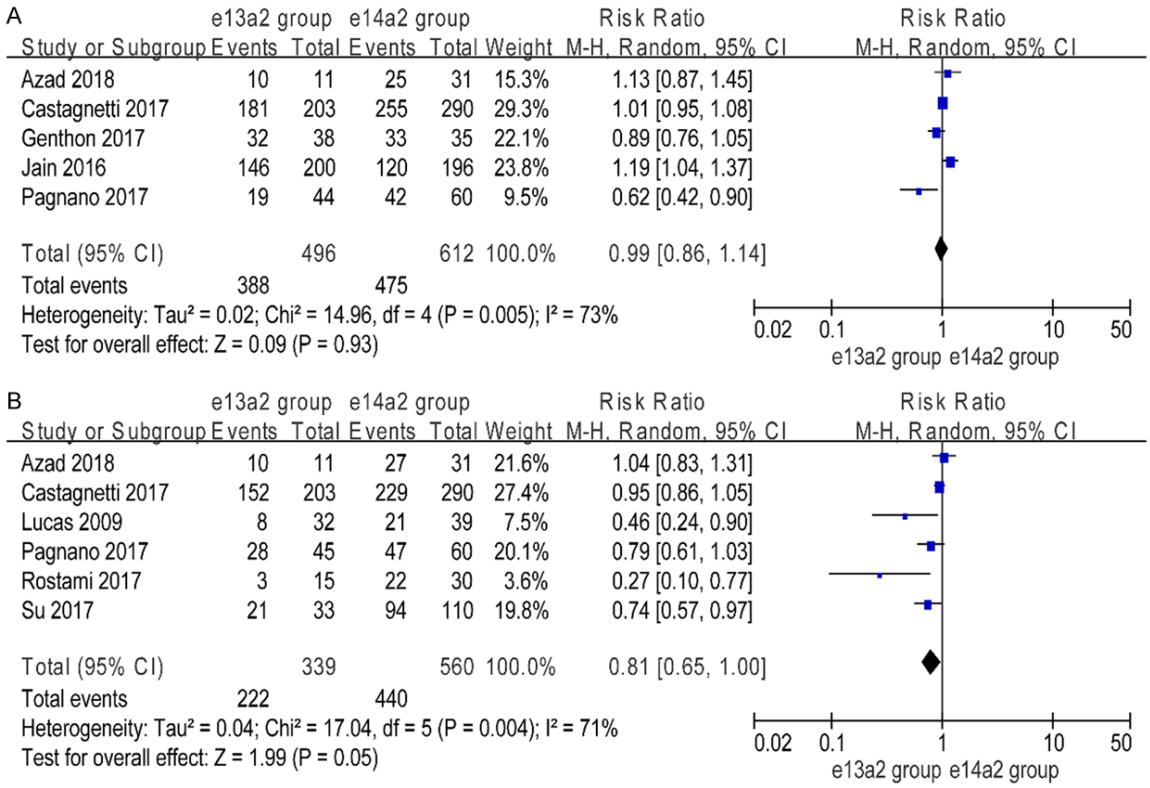

Figure 4. A. The forest plot of the 6-month CCyR rate between the e13a2 and e14a2 transcript; B. The forest plot of the 12-month CCyR rate between the e13a2 and e14a2 transcript.

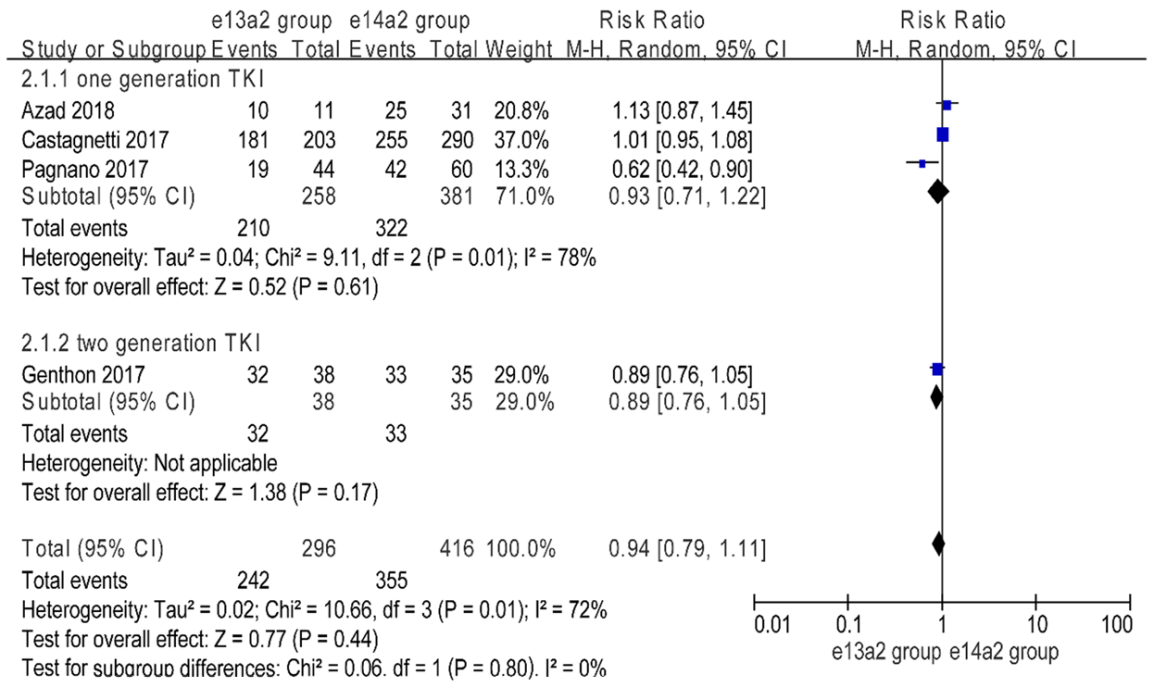

Figure 5. The forest plot of efficacy of TKI on CML patients for the 6-month CCyR rate in the two subgroup.

the above results were stable (**Table 2**). Since less than 10 articles were included in each parameter, no publication bias was used for verification.

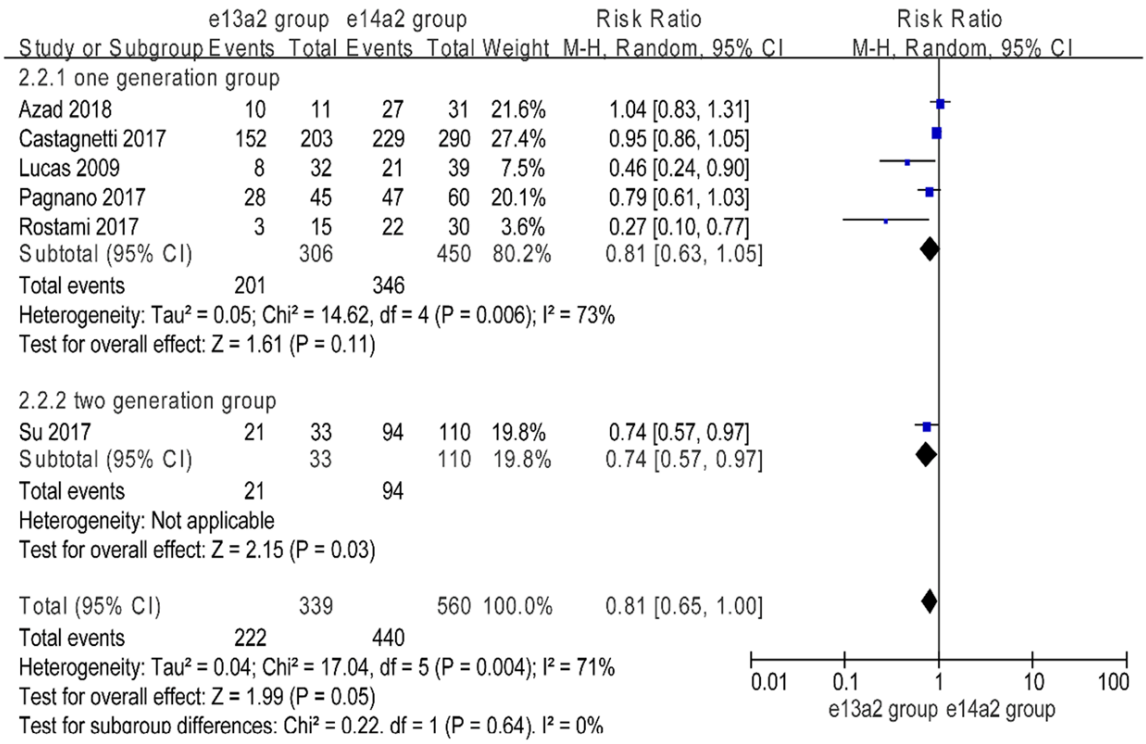

Figure 6. The forest plot of efficacy of TKI on CML patients for the 12-month CCyR rate in the two subgroup.

Table 2. The result of sensitivity analysis

Observation indexes	The random-effect model	The fixed effects model
The 6-month MMR rate	P=0.04	P<0.00001
The long-term MMR rate	P=0.0004	P<0.00001
The 5-year OS rate	P=0.0007	P=0.0007
The 6-month CCyR rate	P=0.93	P=0.42
The 12-month CCyR rate	P=0.93	P=0.0002

Abbreviations: MMR, major molecular response; OS, overall survival; CCyR, complete cytogenetic response.

Discussion

In 1959, Hungerford and Nowell found an abnormal chromosome in CML [22]. The abnormal chromosome was called Philadelphia chromosome that was formed by translocation of ABL gene on chromosome 9 and BCR gene on chromosome 22. The Philadelphia chromosome, the target of TKI therapy, could be found in approximately 95% of CML patients. It could form different transcripts such as e13a2, e14a2, e1a2, e14a3, e8a2 and e6a2, the reason is the variable breakpoints in BCR gene and ABL gene. The most common transcripts were e13a2 and e14a2 transcripts [23].

The e13a2 and e14a2 transcript might present different clinical features. It was reported the incidence of patients with the e14a2 transcript is higher than that the e13a2 transcript [24]. However, Pazymino et al [25] reported that the incidence of patients with the e13a2 transcript was 94.6% and the incidence of e14a2 transcript was 5.4%. Obviously, the result was different from previous reports. We believed that the reason of presenting different results might be demographic differences. We know that the population of the former research mainly involved Caucasians, but the population of the latter research was a mixed ethnic population from these studies. The genetic background and geographic characteristic of above studies were also different. Furthermore, a study found that the e13a2 transcript was dominant among men [24]. Consistent with the above results, studies resulting from India and Italy had also confirmed this conclusion that there were differences in transcript types and sex distribution [18, 26]. Bennour et al [23] found that there was difference in transcript types and age distribution, i.e., patients with e14a2 tran-

script tended to be elderly. However, other studies found that there was no significant differences between transcript types and age distribution [7, 27, 28]. In addition, another study involving 1105 samples found that patients with the e14a2 transcript presented higher platelet levels, however, patients with the e13a2 transcript showed higher leukocyte levels [28]. Deb et al [13] found that patients with the e13a2 transcript had higher Sokal and EUTOS scores.

TKI could significantly improve the prognosis of CML. However, it still faced the problem of the potential for side effects, high costs, non-adherence and so on [2-4]. Many evidence demonstrated that earlier achieving the MMR played a vital role in the "cessation TKI" [5-7]. Some studies had also presented the influence of BCR/ABL transcript type on the MMR during TKI treatment [6, 17, 20, 29]. Therefore, it was very important to screen out the transcript types that had good effects on TKI treatment. Furthermore, it could also help screen out high-risk patients before treatment, provide appropriate treatment options, strengthen monitoring during TKI treatment and detect drug resistance much earlier. The optimum therapy method could also further improve the precise treatment of drugs and efficacy of the TKI drug benefitting from safe drug withdrawal. Finally, it could also provide a new prognostic indicator for the clinic.

Our results showed that patients with the e14a2 transcript could improve the 6-month MMR rate, long-term MMR rate, 5-year OS rate and 12-month CCyR rate. Moreover, the result of sensitivity analysis also showed that the above results were stable and the conclusion was reliable. We held the opinion that patients with the e14a2 transcript might present much better efficacy during TKI treatment.

The structural difference of BCR/ABL transcripts might explain the inconsistent variability in TKI efficacy. The proteins encoded by the e13a2 and e14a2 transcript differed in length by 25 amino acids [30-34]. The additional 25 amino acids, in the e14a2 transcript type, could cause the difference in domain of BCR/ABL kinase that result in better efficacy because of reducing the kinase activity in the e14a2 transcript [20, 34-36]. Another study also confirmed that the extra 25 amino acids was associated with SRC homology domain and DNA binding domain (modulate the kinase activity) [37]. Lucas et al [20] reported that patients with e14a2 transcript presented the lower pCrKL levels that could reduce the kinase activity. Some reports showed that there were more male patients with the e13a2 transcript and they showed a worse prognosis [2, 33, 38]. The reasons for inconsistent variability in TKI efficacy were as follows, the higher platelet counts and the lower probability of disease transformation associated with e14a2 transcripts [7, 28].

In addition, a retrospective study involving 64 patients explored the relationship between different BCR/ABL transcripts and prognosis after cessation TKI. The result suggested that the e14a2 transcript was associated with the higher not-therapy remission rate [39]. Rostami et al [21] showed that the recurrence rate of patients with the e14a2 was lower than that the e13a2 transcript after cessation TKI. Hehlmann et al [40] reported that the earlier the MMR was achieved, the better the prognosis.

The subgroup analysis showed that the one and two generation TKI did not significantly reduce the heterogeneity of CCyR at 6-month. There was no statistically significant difference between the one and two generation TKI subgroup. However, Hughes et al [41] found that the probability of BCR/ABL kinase mutations during the two generation TKI treatment was less than that the one generation TKI. This might be related to the structure of the one and two TKI. The two generation TKI could bind to the activated conformation or non-activated conformation of the ABL kinase domain, which could inhibit TKI activity and inhibit kinase activities (src and c-kit). The subgroup analysis of our study did not find any differences in the one generation and two generation TKI subgroup.

Our study was the first meta-analysis to evaluate the different BCR/ABL transcripts of CML and the efficacy of TKI treatment. A large number of clinical randomized controlled studies are still needed for further confirmation because of the few included literature. However, it could improve the cognition of different transcripts during TKI treatment, and it also provided a new theoretical basis for improving the prognosis of CML.

In conclusion, this study indicated that the 6-month MMR rate, the long-term MMR rate, the 5-year OS and the 12-month CCyR rate were correlated with the BCR/ABL transcript in patients with CML after TKI treatment. The e14a2 transcript performing TKI treatment showed a much better efficacy.

Disclosure of conflict of interest

None.

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