

Original Article

Efficacy and safety of tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia: a meta-analysis

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Received September 3, 2015; Accepted February 2, 2016; Epub February 15, 2016; Published February 29, 2016

Abstract: We performed the present meta-analysis to compare the efficacy and safety of imatinib, dasatinib, nilotinib and bosutinib in the treatment of chronic myeloid leukemia. Literatures were searched in PubMed, Medline, Embase and the Cochrane library to screen citations from January 1980 to June 2015 in this study. The mixed treatment comparison (MTC) meta-analysis within a Bayesian framework was performed by WinBUGS14 software. The proportions of patients achieved complete cytogenetic response (CCyR) and major molecular response (MMR) at 12 month and 24 month were analyzed respectively. Overall survival (OS) and the grade 3/4 hematologic adverse events were also analyzed. The results of our meta-analysis showed that dasatinib (OR=2.15, 95% CI 1.25 to 3.62) and nilotinib (OR=2.79, 95% CI 1.84 to 4.24) had higher MMR than imatinib at 12 month. The four TKIs have similar MMR at 24 month and CCyR at 12 month and 24 month. The 24 month OS were not shown to be significant difference between these TKIs. We also analyzed the grade 3/4 hematologic adverse events at 24 month, the results showed that the TKIs have similar adverse events. Therefore, we found that imatinib, dasatinib, nilotinib and bosutinib have similar CCyR and MMR at 24 month and similar CCyR at 12 month. Furthermore, dasatinib and nilotinib have higher MMR than imatinib at 12 month. There was no significant difference between these TKIs in the OS and the grade 3/4 hematologic adverse events.

Keywords: Chronic myeloidleukemia, tyrosine kinase inhibitors, drug safety, efficacy, meta-analysis

Introduction

Chronic myeloid leukemia (CML) is characterized by an active BCR-ABL1 fusion protein produced by the t (9;22) translocation known as the Philadelphia chromosome (Ph) [1]. The incidence rate of CML is one and per 100,000 people per year. Allogeneic stem cell transplant could provide a long-term survival, but many patients were not eligible for transplant. For those patients, interferon- α (IFN- α), hydroxyurea or chemotherapy was the first line therapy with survival of four to six years [2].

Imatinibmesylate was an inhibitor of the oncogenic BCR-ABL fusion protein in CML [3]. The long-term study for International Randomized Study of Interferon and STI571 predicts that patients who response to imatinib therapy may have a mean survival estimate of approximate-

ly 20 years [4]. However, many patients receiving imatinib do not have the desired treatment goals. About 35% of patients treated with imatinib achieved the major molecular response at the first year [5, 6].

Second generation BCR-ABL1 tyrosine kinase inhibitors (TKIs), dasatinib and nilotinib, are approved for the treatment of CML [7]. Compared with imatinib, dasatinib and nilotinib have superior rates of cytogenetic and molecular response in newly diagnosed CML patients [5, 6]. These drugs were also approved for first line use by the USA Food and Drug Administration and European Medicines Agency.

Bosutinib is an oral, dual Src/ABL TKI with more potent inhibitory activity against Bcr-Ab1 than imatinib in CML cell lines [8, 9]. The ongoing phase 3 trials comparing the efficacy and safe-

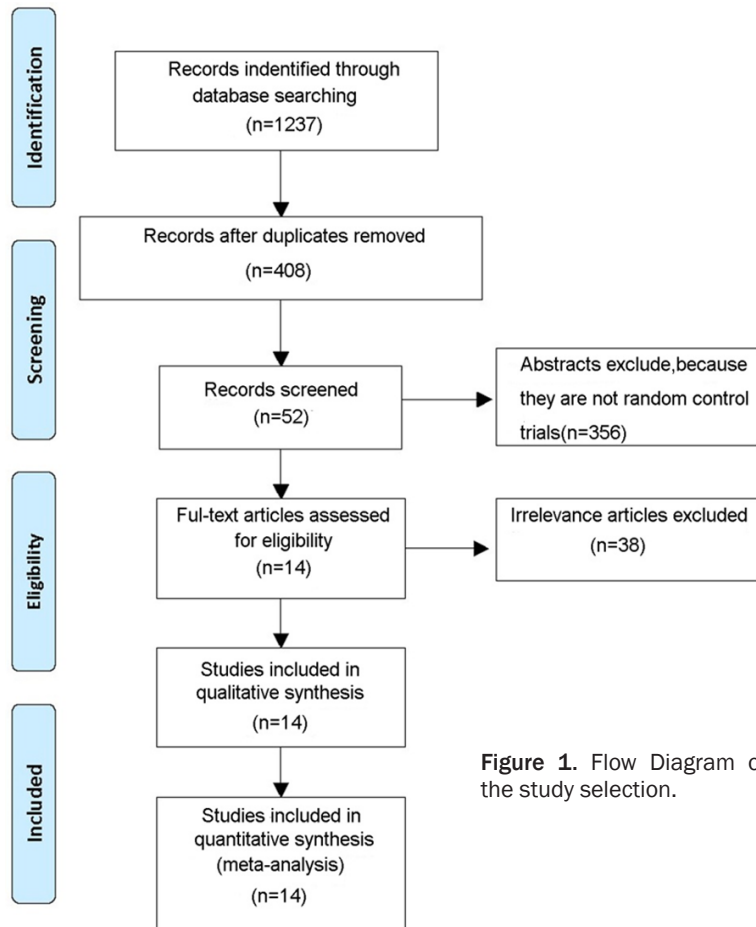


Figure 1. Flow Diagram of the study selection.

ty of bosutinib and imatinib in newly diagnosed CML patients showed that bosutinib had a superior rate of major molecular response (MMR) versus imatinib [10]. Bosutinib also has the shorter median times to complete cytogenetic response (CCyR) and MMR than imatinib.

In the absence of head to head trials of dasatinib, nilotinib and bosutinib in newly diagnosed CML, we therefore performed a network meta-analysis comparing the efficacy and safety of imatinib, dasatinib, nilotinib and bosutinib in CML treatment.

Methods

Search strategy and selection criteria

Three databases (PubMed, Embase and Medline) were screened to obtain citations from January 1980 to June 2015 for inclusion in this study. The key words “chronic myeloid leukemia” and (bosutinib or dasatinib or imatinib or nilotinib) were used to search relevant cita-

tions. We included those studies meeting the following criteria: (1) patients with newly diagnosed CML; (2) patients greater than 18 years old; (3) studies published in English; (4) studies provided the data at least with one of main outcomes, including CCyR, MMR, overall survival (OS) and adverse events; (5) randomized controlled trials.

Publication bias

Given the small numbers of studies included in this meta-analysis, publication bias was not formally assessed.

Data extraction and quality assessment

Two reviewers extracted the data from included studies independently. The following information was extracted from each study: the trial name; the number of patients; the age of patients; the main outcomes (CCyR, MMR,

OS and adverse events); the treatment duration. The Jadad score was used to assess the quality of the included studies.

Data analysis

To evaluate the relative effectiveness of each medicine, a mixed treatment comparison (MTC) meta-analysis within a Bayesian framework was performed. CCyR and MMR at 12 month and CCyR, MMR and OS at 24 month were used to evaluate the efficacy in CML. For all Bayesian analyses, Markov-chain-Monte-Carlo methods were used. A random effect model was used to estimate the odds ratios (ORs) as the measure of relative treatment effect [11]. We carried out 60,000 iterations. The first 10,000 iterations were discarded after the burn-in period and estimates were based on the subsequent 50,000 ones. Data analysis was performed by WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

Tyrosine kinase inhibitors in treatment of CML

Table 1. Main characteristics of the included studies

Study	Interventions	No. of patients	Age Media (range)	Gender M/F	Hasford risk (No.)			WBC (10 ⁹ /L) Media (range)	Platelets (10 ⁹ /L) Media (range)	Follow up years	Jadad-score
					Low	Intermediated	High				
DASISION	Dasatinib 100 mg	259	46 (18-84)	144/115	86	124	49	25.1 (2.5-493)	448 (58-1880)	3	5
	Imatinib 400 mg	260	49 (18-78)	163/97	87	123	50	23.5 (1.4-475)	390 (29-2930)		
ENESTed	Nilotinib 300 mg	282	47 (18-85)	158/124	103	101	78	23 (2-247)	424 (90-3880)	3	5
	Imatinib 400 mg	283	46 (18-80)	158/125	104	101	78	26 (3-482)	375 (66-2232)		
ENESTed China	Nilotinib 300 mg	134	41 (18-76)	91/43	69	44	21	-	-	2	5
	Imatinib 400 mg	133	39 (19-74)	81/52	69	43	21	-	-		
S0325Intergroup Trial	Dasatinib 100 mg	123	47 (18-90)	74/49	44	40	39	89 (3-410)	363 (100-810)	3	3
	Imatinib 400 mg	123	50 (19-89)	72/51	44	45	34	52 (0.3-401)	378 (109-1390)		
BELA	Bosutinib 500 mg	250	48 (19-91)	149/101	88	117	45	-	-	2	5
	Imatinib 400 mg	252	47 (18-89)	135/117	89	118	45	-	-		

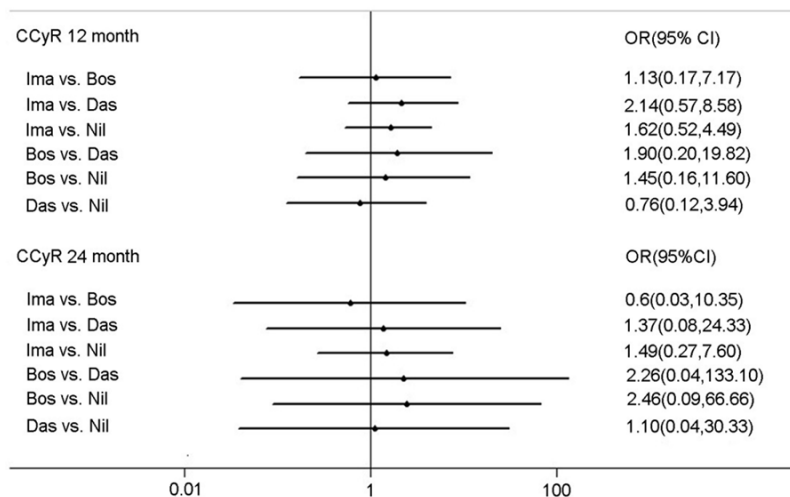


Figure 2. Forest plots of OR comparing CCyR for patients who receive TKIs. Bos, bosutinib; Das, dasatinib; Ima, imatinib; Nil, nilotinib.

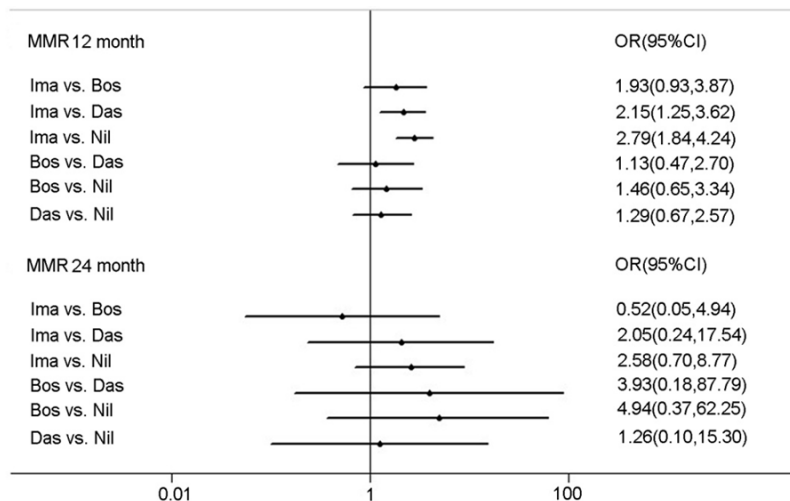


Figure 3. Forest plots of OR comparing MMR for patients who receive TKIs. Bos, bosutinib; Das, dasatinib; Ima, imatinib; Nil, nilotinib.

Results

Search results and characteristics

A total of 1237 citations were obtained via database searches; fourteen met the inclusion criteria for this study (**Figure 1**). A total of 2380 patients have been involved, in which 250 subjects were treated with bosutinib, 382 subjects with dasatinib, 1051 subjects with imatinib and 697 subjects with nilotinib. The information in these citations is summarized in **Table 1**. All fourteen studies have been assessed by Jadad score system with score no less than 3 (**Table 1**).

Adverse events

A total of 4 studies reported the grade 3/4 hematologic adverse events at 24 month. The MTC meta-analysis showed that the four TKIs have similar grade 3/4 hematologic adverse events at 24 month (**Figure 5**).

Discussion

Bayesian approaches based on Bayesian statistical framework are standard in network meta-analysis. It could be used to rank treatments based on effectiveness or other measures. Currently there are three randomized

Complete cytogenetic response

A total of 5 studies reported the CCyR at 12 month and 4 studies reported the CCyR at 24 month. The MTC meta-analysis showed that these drugs had similar CCyR in CML patients at both 12 month and 24 month (**Figure 2**).

Major molecular response

A total of 5 studies reported the MMR at 12 month and 4 studies reported the MMR at 24 month. The MTC meta-analysis showed that dasatinib (OR=2.15, 95% CI 1.25 to 3.62) and nilotinib (OR=2.79, 95% CI 1.84 to 4.24) have a higher MMR rate compared with imatinib at 12 month. However, these drugs had similar MMR in CML patients at 24 month (**Figure 3**).

Overall survival

A total of 4 studies reported the OS at 24 month. The MTC meta-analysis showed that there was no significant difference between these TKIs (**Figure 4**).

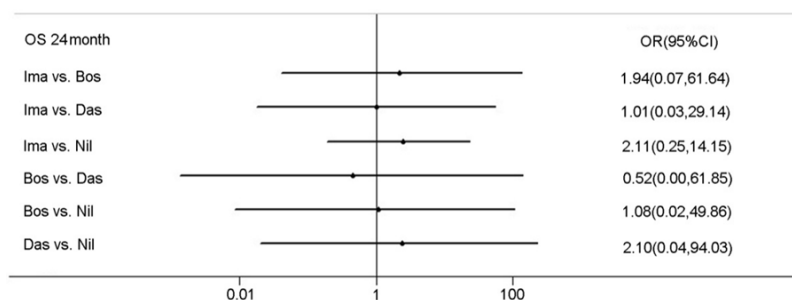


Figure 4. Forest plots of OR comparing OS for patients who receive TKIs. Bos, bosutinib; Das, dasatinib; Ima, imatinib; Nil, nilotinib.

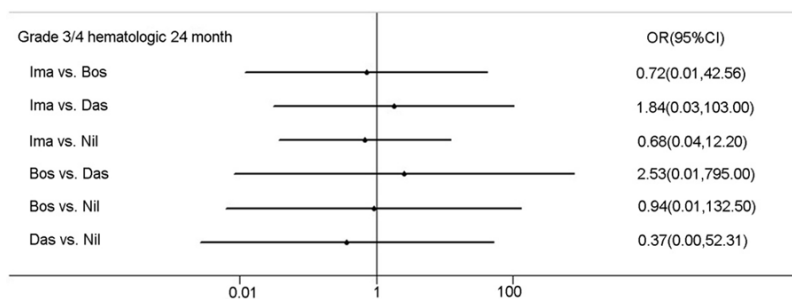


Figure 5. Forest plots of OR comparing grade 3/4 hematologic adverse events for patients who receive TKIs. Bos, bosutinib; Das, dasatinib; Ima, imatinib; Nil, nilotinib.

controlled trials in CML treatment that include nilotinib or dasatinib or bosutinib: the ENESTnd Trials [6, 12, 13] and ENEST China Trial [14] comparing nilotinib and imatinib; the DASISION Trials [5, 15-18] and the S0325 Intergroup Trial [19] comparing dasatinib and imatinib; the BELA Trial [10, 20, 21] comparing bosutinib and imatinib. All four trials are multicenter, open-label, randomized trials.

The results of our meta-analysis showed that dasatinib and nilotinib had higher MMR than imatinib at 12 month. The four TKIs have similar MMR at 24 month and CCyR at 12 month and 24 month. The 24 month OS was not shown to be significant difference between these TKIs. We also analyzed the grade 3/4 hematologic adverse events at 24 month, the results showed that the TKIs have similar adverse events.

To our knowledge, this is the first network meta-analysis comparing the efficacy and safety of currently available TKIs. Three previous indirect comparisons have been conducted for dasatinib and nilotinib in CML patients. Signorovitch

et al. [22] found that nilotinib has higher MMR than dasatinib based on ENESTnd and DASISION. However, Mealing et al. [23] study including data from ENESTnd, DASISION and S0325 found no significant difference in 12-month MMR between nilotinib and dasatinib which consisted with our findings. A recent network meta-analysis including all currently published trials data also indicated that there is no significant difference between nilotinib and dasatinib on MMR at 12 month [24].

However, it should be noted that there were some limitations in our study. Firstly, the small sample size and lack of head-to-head trials may increase the uncertainty

of the results. Secondly, we could not assess the publication bias. Thirdly, a potential weakness of this meta-analysis was caused by the fact that the included trials were not double blinded. Despite these limitations, we believed that our analysis could contribute to clinical decision making of the CML treatment.

In conclusion, imatinib, dasatinib, nilotinib and bosutinib have similar CCyR and MMR at 24 month and similar CCyR at 12 month. Furthermore, dasatinib and nilotinib have higher MMR than imatinib at 12 month. There was no significant difference between these TKIs in the grade 3/4 hematologic adverse events. Moreover, head-to-head comparisons, continuous data collection and benefit-risk assessment are needed to confirm our findings.

Acknowledgements

This study was supported by Grants from the National Natural Science Foundation of China (No. 81372391, 81300443, 81529001 and 81570190), and Shanghai Tenth People's Hospital Funds (No. 040113015).

Disclosure of conflict of interest

None.

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