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REVIEW ARTICLE

Treatment after failure of frontline therapy of chronic myeloid leukemia in chronic phase including allogeneic hematopoietic stem cell transplantation

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Abstract

The treatment outcomes of chronic myeloid leukemia in chronic phase (CML-CP) have dramatically improved with comparable life-expectancy to average of general population in tyrosine kinase inhibitor (TKI) era. However, less than a half of patients who started with TKI can remain on frontline TKI. The reasons of switching TKI can be either intolerance or the lack of efficacy. Although a kinase domain (KD) mutation can guide to select salvage TKI from the point of view on the efficacy of TKIs, many factors need to be considered before choosing next-line TKI such as the high-risk features of CML, the adverse events with prior TKI, and the comorbidities of patients. The therapeutic options for CML-CP after failing frontline TKI due to treatment failure or suboptimal responses will be reviewed including allogeneic hematopoietic stem cell transplantation.

Key Words Chronic myeloid leukemia, Tyrosine kinase inhibitors, Ponatinib, Asciminib, Allogeneic hematopoietic stem cell transplantation

INTRODUCTION

The survival of chronic myeloid leukemia (CML) has been dramatically improved in the era of tyrosine kinase inhibitors (TKI). With the introduction of imatinib, the first generation of *BCR::ABL1* TKI, the survival rates of CML patients has increased to about 80% at 10 years and the life-expectancy could be comparable to the average of general population [1, 2]. However, a significant number of CML patients treated with TKIs require next line of treatment due to intolerance or failure to achieve the optimal response. About 60% of patients who initially started with imatinib and 70–80% with second generation TKIs (2G-TKIs) such as dasatinib and nilotinib remain in optimal response durably [2]. However, if patients with CML in chronic phase (CML-CP) are on third or beyond line of treatment, the survival rate was reported only about 50% or lower at 5 years [3]. This brief review will focus on the therapeutic options including allogeneic hematopoietic stem cell transplantation (allo-HSCT) for CML-CP patients who failed frontline TKIs due to the lack of efficacy than the intolerance.

REASONS TO DISCONTINUE FRONTLINE TYROSINE KINASE INHIBITORS

The sensational success of imatinib compared to interferon and low dose cytarabine has established imatinib as the frontline therapy for CML patients [4]. However, after follow-up duration of 10 years only about a half of patients (267 of 553, 48.3%) in imatinib group could complete treatment with imatinib including a tenth of patients who withdrew the consent. While adverse event became the reason to discontinue for 7% of patients, 16% of patients had to discontinue imatinib due to an unsatisfactory therapeutic effect and about 7% of patients had progressed to the advanced phase of CML As major molecular response (MMR, a 3-log reduction of *BCR::ABL1*) has been well correlated with survival outcomes, MMR became the surrogate goal to primarily achieve for long term survival. Imatinib has been reported to have the rate of MMR by 12 months between 22% and

40%, which is somewhat disappointing as the most of patients with suboptimal responses are considered for the salvage therapy [5-10].

The 2G-TKIs as frontline therapy showed higher rate of MMR at 12 months compared to imatinib; 46% in dasatinib group and 28% in imatinib group from DASISION trial [11]; 44% in nilotinib group and 22% in imatinib group from ENESTnd trial [9]; 47% in bosutinib group and 37% in imatinib group from BFORE trial [5]. The superiority of achieving MMR was translated to the lower rate of discontinuation due to treatment failure, suboptimal responses or disease progression; 13% in dasatinib group and 19% in imatinib group from DASISION trial [11]; 13% in nilotinib group with 300 mg twice daily-dosing schedule and 25% in imatinib group from ENESTnd trial [12]; 11% in bosutinib group and 33% in imatinib group [13].

Nonetheless, the discontinuation rate of 2G-TKIs and imatinib were similar because of higher incidence of intolerance with 2G-TKIs [11, 13, 14]. After 5-year follow-up of DASISION, 21% of dasatinib-treated patients had to discontinue the study drug due to intolerance or any adverse events (AEs) compared to 9% of imatinib-treated patients [11]. From ENESTnd trial, AEs were the reason for discontinuation for 53 of 282 patients (19%) in nilotinib group and 43 of 283 patients (15%) in imatinib group while two thirds of each treatment arm could not complete treatment duration [14]. The 5-year follow-up of BFORE trial also showed similar rates of treatment discontinuation with bosutinib (40.3%) and imatinib (41.9%) [13]. The AEs regardless of relation to treatment were the reason of discontinuation for 67 patients of 268 (25%) in bosutinib group, while for 33 of 265 (12%) in imatinib group [13]. Most common AEs leading to discontinuation were pleural effusion (6%) of dasatinib, cardiovascular events (7.5%) of nilotinib with 300 mg twice-daily dosing schedule, and increased ALT (5%) of bosutinib [11, 13, 14].

BCR::ABL1 KINASE DOMAIN MUTATIONS EMERGING AFTER EXPOSURE OF TYROSINE KINASE INHIBITORS

Among patients treated with imatinib, 43% to 63% of patients were detected mutations of *BCR::ABL1* kinase domain (KD) [15-18]. The most common mutations were T315I, G250E, M244V, M351T, and E255K/V [19]. T135I mutation, the "gatekeeper" mutation, occurred in 10% to 24% of patients with imatinib [15-18].

Mutations of KD were also developed in patients treated with 2G-TKI. DASISION trial performed *BCR::ABL1* mutation testing at the time of discontinuation including study closure and identified specific mutations on 15 of dasatinib arm (N=258) and 18 of imatinib arm (N=258) after 5-year follow-up [11]. Among 28 patients with disease progression or treatment failure of dasatinib arm, 13 patients had detected *BCR::ABL1* mutations including 7 of T315I [11]. ENESTnd trial was tested *BCR::ABL1* mutation at baseline, 5-fold increase in *BCR::ABL1* levels, lack of MMR at 12 months, loss of MMR, or treatment discontinuation [20]. The 3-year follow-up of ENESTnd reported that *BCR::ABL1* mutations were detected in 10 patients with nilotinib 300 mg twice daily, 8 patients with nilotinib 400 mg twice daily, and 20 patients with imatinib 400 mg once daily [20]. The incidence of T315I mutations was similar in 3 treatment groups (4 in nilotinib 300 mg twice daily, 2 in nilotinib 400 mg twice daily, and 3 in imatinib 400 mg once daily) [20]. The difference on emergent mutations between nilotinib arms and imatinib arm was continuously observed by 5-year follow-up [12]. In BFORE trial, 2.2% (6 of 114) of bosutinib group and 4.5% (12 of 131) of imatinib group had detectable mutations at suboptimal response, treatment failure or at the end of treatment [13]. Five out of 6 detected from bosutinib group and 1 of 12 from imatinib group were T315I mutation [13].

TYROSINE KINASE INHIBITORS AFTER FAILURE OF FRONTLINE THERAPY DUE TO RESISTANCE

If CML-CP patients discontinue frontline TKIs due to either intolerance or lack of efficacy, selecting next-line TKI becomes complicated since many aspects as a whole need to be considered including mutation profiles of KD, the efficacy and tolerability of TKIs, comorbidities of patients, and the eligibility of National Health Insurance in some countries if no KD mutation is identified. The second-line treatment or beyond for CML-CP is more challenging if the reason of switching TKI is the lack of efficacy as cumulations of evidences on 2G-TKIs as salvage therapy are somewhat disappointing. Dasatinib as second-line therapy for imatinib resistant CML-CP only demonstrated 43% of MMR with 65% of overall survival (OS) at 7 years [21]. Nilotinib showed similar outcomes of 45% of complete cytogenetic response (CCyR) with 78% of OS after 48-month follow-up [22]. 2G-TKIs as third-line therapy including at least 1 prior 2G-TKI treatment demonstrated even lower activity of disease control with the rate of CCyR of 22% to 25% [23]. Survivals also decreased with later line of treatment as correlated to low rate of cytogenetic and molecular responses. A retrospective study of a single institution reported dropping OS at 5 years with each subsequent line of treatment from 80% to 53% to 38% if patients were on second-line, third-line, and fourth or beyond-line of TKIs, respectively [3].

For the elderly patients, the choice of salvage TKI after failing frontline therapy becomes even more difficult as the comorbidities have to be taken into account as major concerns of safety include cardiovascular toxicities and effusions in major organs. A small phase 2 study of bosutinib from Italian group suggested the gradual dose wrap-up of bosutinib could be an option for elderly CML patients (≥60 yr old) after failure of frontline TKI (imatinib 83%, dasatinib 11% and nilotinib 6^) [24]. The study was designed to start bosutinib 200 mg for 2 weeks, then to increase 300 mg. If *BCR::ABL1* >1% at 3 months, bosutinib was increased to 400 mg in absence of relevant toxicity. Among 63 patients enrolled

(median age 73 yr, range 60–90) 37% of patients failed to frontline TKI due to resistance. The rate of MMR by 12 months among patients with resistance was 52% and 65% with intolerance. After median follow-up of 9 months, 51 of 63 patients remained on bosutinib [24]. A multicenter, retrospective analysis reported the outcome of salvage dasatinib for elderly CML-CP (>60 yr old) patients intolerant/resistant to imatinib [25]. Majority of patients (89.6%) were resistant to imatinib and 22% of patients received dasatinib as third line therapy. Among 122 evaluable patients, 49% achieved complete cytogenetic response (CCyR) and 38 of 60 patients in CCyR achieved MMR. 15% patients discontinued dasatinib permanently due to toxicity [25].

In salvage setting, ponatinib and asciminib can offer better therapeutic options than another 2G-TKI. The phase 2 trial of ponatinib for Philadelphia chromosome-positive leukemia (PACE trial) demonstrated the effectiveness on CML-CP patients (N=270) who failed at least 2 prior TKIs [26]. With 24% of T315I positive CML included, 40% of patients achieved MMR with 73% of OS at 5 years [26]. The safety concern with arterial occlusive events (AOEs), however, had to withdraw ponatinib from the market transiently [26, 27]. To reduce the risk of AOEs while still maintaining the potent activity on disease control, the OPTIC trial navigated to find optimal strategy of dosing ponatinib [28]. The OPTIC trial was designed to start at 3 different dose levels of 45 mg/day, 30 mg/day, or 15 mg/day and to deescalate the maintenance dose of 15 mg/day in higher-dosing cohorts once *BCR::ABL1* <1% (MR2) was achieved [28]. While the cohort with starting dose of 15 mg/day achieved 25.3% of MR2 by 12 months, the cohort with 45 mg/day and 30 mg/day achieved 51.6% and 35.5% of MR2 by 12 months, respectively [28]. The treatment-emergent AOEs (TE-AOEs) per 100 patient-years were 9.6%, 5.3%, and 3.2% for the cohort of 45 mg/day, 30 mg/day, and 15 mg/day, respectively [28]. The beneficial effect of higher starting dose on achieving MR2 was more prominent with high-risk characteristics such as T315I mutation or resistance to prior TKIs [28].

Most recently, asciminib, a myristoyl pocket inhibitor of ABL, was approved for CML-CP previously treated with 2 or more TKIs [29]. The ASCEMBL trial was a randomized, open-label phase 3 trial to compare asciminib to bosutinib for CML-CP previously treated with ≥2 TKIs [30]. Patients were randomized to receive either asciminib 40 mg twice daily or bosutinib 500 mg once daily in 2:1 ratio [30]. Asciminib arm demonstrated superiority with 25.5% of MMR rate at 24 weeks to bosutinib (13.2% of MMR rate at 24 wk) [30]. After longer follow-up, the rate of MMR increased to 37.6% with asciminib and 15.8% with bosutinib at 96 weeks [31]. The difference of MMR rate was shown wider in patients who discontinued the last prior TKI due to the lack of efficacy than those due to the intolerance (23.1% vs. 14.5%) [31]. Even though there were 8 patients who developed AOEs on asciminib arms as compared to 1 patient on bosutinib arm, AEs leading to the treatment discontinuation were more frequent on bosutinib arm (26.3%) than asciminib arm (7.7%) [31]. Overall, asciminib showed superior treatment outcomes to bosutinib for CML-CP failing at least 2 prior TKIs with higher rate of MMR with benefit of 12% at 24 weeks and 22% at 96 weeks [30, 31].

To briefly summarize, if CML-CP patients fail frontline imatinib due to lack of efficacy, the choice of second line TKI can be a 2G-TKI based on KD-domain mutations in absence of T315I mutation. However, the molecular or cytogenetic responses of second line 2G-TKI are less than 50% and the long-term survival can be expected around 70%. Patients who failed frontline 2G-TKI or beyond now have options of ponatinib and asciminib. Although there is no head-to-head comparison of two, the matrix of choice in clinical practice has been suggested in preference to ponatinib with high refractoriness and asciminib with high cardiovascular risks based on the resistance severity and cardiovascular risks [32].

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CHRONIC PHASE CHRONIC MYELOID LEUKEMIA

The role of allo-HSCT for long term survival and probable cure for patients with CML-CP has been established in pre-TKI era [2, 33]. Graft-versus-leukemia effect in CML has been suggested based on the studies showing donor lymphocyte infusion could salvage the relapsed disease after allo-HSCT [34, 35]. However, the activity of allo-HSCT for CML-CP has drastically declined with the introduction of TKIs [36].

When to consider proceeding allo-HSCT, the greatest concern is the transplant-related mortality (TRM) which has been reported about 40% and the long-term survival of allo-HSCT for CML was eventually about 50% or less [33, 37]. As repeated failing of TKIs worsened survival outcomes of CML-CP patients, allo-HSCT could be brought up as a treatment option at some point. While 5-year OS was reported at 40% among CML-CP patients in fourth or beyond line of treatment from a retrospective analysis, 5-year OS of allo-HSCT for CML could be reached to 70% in highly selected patients [3, 33]. The retrospective analysis of the largest cohort from the European group for Blood and Marrow Transplantation included 13,416 patients from 1990 to 2004 [33]. Stage, donor type, time interval to transplantation, age, and donor-recipient sex combination were identified as the risk factors and patients with a risk score of 0 or 1 showed 60% of leukemia-free survival and 71% of OS at 5 years with 21% of TRM [33].

The most recent update of European LeukemiaNet recommendations suggested to assess for allo-HSCT when to become resistance to 2G-TKI (first or second line) in CML-CP [6]. Failing to ponatinib after 3 months' treatment also was indicated for early allo-HSCT [6].

CONCLUSION

After first introduction of imatinib, the treatment outcomes and survivals of CML has been impressively improved. However, a half of patients change frontline TKI due to intolerance or lack of efficacy. The choice of second line TKI or beyond is difficult as every aspect of the risk of CML, tolerability, and comorbidities of patients has to be taken into account other than the efficacy of TKIs. Although ponatinib and asciminib are potent *BCR::ABL1* inhibitors and can salvage CML-CP patients in third-line or beyond setting, there are unmet needs with a significant risk for progression to advanced phases of CML and allo-HSCT still can be a viable option for the carefully selected patients who are resistant to multiple TKIs.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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