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Blood 142 (2023) 3179–3180

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

632.CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Lower-Initiating Dose of Bosutinib for Resistant or Intolerant to Prior Therapy Chronic Myeloid Leukemia Patients (BOGI trial): A Single-Arm, Multicenter, Phase II Trial

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Introduction:
The introduction of ABL1 tyrosine kinase inhibitors (TKIs) has markedly improved the survival outcomes in patients with chronic phase chronic myeloid leukemia (CML-CP). Second-generation TKIs are highly active for patients with newly diagnosed and resistant/intolerant CML-CP. Although bosutinib is generally safe, drug-related toxicities (DRTs) such as diarrhea or increased transaminase leading to treatment discontinuation, are often observed. The standard initial daily dosage of bosutinib is 400 mg for newly diagnosed or 500 mg for resistant/intolerant patients with CML-CP, whereas some experts suggest lower dose (200-300 mg) initiation is recommended to reduce adverse events (AEs). However, the safety and efficacy of lower dose initiation of bosutinib are unknown. Hence, we conducted a phase 2 study of BOsutinib Gradual Increase as a second/third-line treatment for CML-CP (BOGI trial, UMIN 000032282) to clarify whether a lower initiating dose of bosutinib (200 mg daily) would reduce discontinuation or interruption of treatment due to DRTs.

Patients and methods
We included CML patients who developed at least one line of treatment failure (resistant or intolerant), aged >18 years with an ECOG performance status of 0-2 and adequate organ function. After enrollment, the patients initiated 200 mg of bosutinib daily; subsequently, dose escalation was performed by 100 mg daily (up to 500 mg daily) every 2 weeks if no grade 3 or higher AEs occurred. *BCR::ABL1* mRNA levels were measured by the standardized international scale at a central laboratory at 3, 6, 9, and 12 month since treatment initiation. The primary endpoint was the treatment discontinuation rate due to DRTs at 12 months. Secondary endpoints included the treatment interruption rate, mean bosutinib dosage, dosing days and relative dose intensity until 12 months, achievement of cytogenetic response (CCyR), cumulative rates of major molecular response (MMR) or deep molecular response (DMR). Sample size calculation was performed by research and biostatistics SWOG statistical tools (at null proportion = 0.32, alternative proportion = 0.14, one-sided α error = 5% and β error = 20%, power 80%) with the discontinuation rate of the previous Japanese phase 1/2 study of bosutinib as a reference (Nakaseko C, *et al. Int J Hematol.* 2015). Considering protocol deviations, sample size was 35 participants.

Results
Between Feb 4, 2019, and May 24, 2022, 35 patients enrolled from four Japanese hospitals. The median age was 61 years (range, 26 - 81 years); 19 patients were male and 16 were female and 16, 12, and 7 patients had low,intermediate, and high Sokal scores, respectively. Ten patients had hypertension, five had diabetes millitus, three had chronic heart disease, two had solid tumor, and one had cerebrovascular disease, respectively. Numbers of patients with previous TKIs were one for 19 (54%), two for 12 (34%) and three for 4 (11%), respectively and prior TKIs are imatinib (8, 23%), dasatinib (27, 77%), nilotinib (16, 46%) and bosutinib (1, 3%), respectively. In the intention to treat population, the bosutinib discontinuation rate at 12 months was 25.7% (95% CI, 15.6-39.3%) which is significantly lower than that of the previous report (v.s. 43.0%, p=0.019). Similarly, bosutinib discontinuation rate due to DRTs was 11.4% (95% CI, 5.2 - 23.2%), which is also significantly lower (v.s. 32%, p =

0.005). These results suggest lower initiating dose of bosutinib reduced bosutinib discontinuation rate due to DRTs, thus the primary endpoint was met.
A total of 22 patients (62.9%) interrupted bosutinib at least once. Median bosutinib dosage, bosutinib dosing days and relative dose intensity until 12 months were 391.7 (204.9-477.3) mg/day, 351.0 (20-365) days and 78% (41-95), respectively. 28 patients (80.0%) achieved cytogenetic response (CCyR) at 6 months; cumulative incidence of MMR and DMR at 12 months were 23 (65.7%; 95%CI, 49.2-79.2%) and 15 (42.9%; 95%CI, 28.0-59.1%), indicating these secondary endpoints were comparable with the previous report. Grade 3 to 4 transaminase elevation was 20% which is comparable with the previous report (v.s. 29%, p=0.427), while a lower rate of diarrhea (3%; v.s. 25%, p=0.009) was notable.

Conclusion

The lower initiating dose followed by a gradual dose increase of bosutinib reduced the drug discontinuation rate due to severe DRTs, especially diarrhea, while efficacy was assured.

Disclosures Takahashi: *Otsuka Pharmacuetical:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Mochida Pharma:* Research Funding; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Asahi-Kasei:* Research Funding; *Astellas pharma:* Other: Commissioned research and joint research , Research Funding. **Ikezoe:** *AsahiKasei Pharma, Nippon Shinyaku Co., Ltd:* Research Funding; *Bristol-Myers Squibb Company, Novartis Pharma KK, Pfizer Japan Inc., Takeda:* Honoraria. **Ichinohe:** *Ono Pharmaceutical Co.:* Honoraria; *AsahiKasei Pharma Co.:* Honoraria, Research Funding; *Kyowa Kirin:* Research Funding; *Novartis:* Honoraria; *Sumitomo Pharma Co:* Honoraria, Research Funding; *Abbvie Co.:* Honoraria, Research Funding; *Nippon Shinyaku Co.:* Honoraria, Research Funding; *Wakunaga Pharmaceutical Co., Ltd.:* Research Funding; *Nippon Kayaku Co.:* Honoraria; *Repertoite Genesis Inc.:* Research Funding; *Takeda Pharmaceutical Co.:* Honoraria; *Chugai:* Honoraria, Research Funding. **Kimura:** *OHARA Pharmaceutical Co., Ltd.:* Honoraria, Patents & Royalties, Research Funding.

Table 1. Treatment status and reasons for discontinuation in study patients

	n (%)	
Received treatment	35	(100)
Continued treatment	26	(74.3)
Discontinued treatment	9	(25.7)
Drug-related adverse event	4	(11.4)
Treatment failure or Disease progressed	2	(5.7)
Withdrew consent	2	(5.7)
Other	1	(2.9)

Figure 1. Efficacy of bosutinib treatment

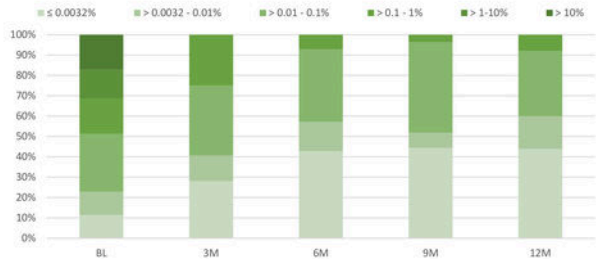

Figure 1

https://doi.org/10.1182/blood-2023-174594