

BCL2L11 (*BIM*) deletion polymorphism, rather than *BIM* SNP, is an effective predictor of early molecular relapse after ABL tyrosine kinase inhibitor discontinuation in patients with chronic myeloid leukemia

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Abstract

New biomarkers are becoming available for the identification of patients who are suitable for the future discontinuation of ABL TKI treatment. We have shown a specific association between the *BIM* deletion polymorphism and the clinical outcome after ABL TKI treatment discontinuation in patients with long-lasting molecularly undetectable residual disease. Thirty-two CML patients were included in this study. The cumulative incidence of loss of MMR was estimated as 25.0% at 12 months and 31.3% at 24 months. We found that the *BIM* deletion polymorphism is a better predictor than *BIM* SNP of early molecular relapse after TKI treatment discontinuation in CML patients. We have reached the final stage of establishing the criteria for the discontinuation of ABL TKI treatment in CML patients. We are beginning to understand the strategies required for the successful discontinuation of ABL TKI treatment.

Imatinib and the new ABL tyrosine kinase inhibitors (TKIs) have become the most successful class of targeted therapies for cancer, exceeding all projected survival expectations. With ABL TKI treatment, the annual all-cause mortality rate of chronic myeloid leukemia (CML) declined to 2% compared with a historical rate of 10% to 20%, and the estimated 10-year survival rate increased from 20% to greater than 80% [1]. The discontinuation of imatinib is currently being investigated for patients with CML who are in prolonged complete molecular response (CMR) [2,3]. In 2010, Mahon *et al.* reported a pilot study evaluating the feasibility and safety of imatinib discontinuation in patients with CMR of longer than 2 years and observed that half of the patients experienced molecular relapse during the 6 months after treatment discontinuation [2]. No late relapse was observed in the remaining patients during an extended follow-up period of longer than 4 years. Therefore, the discontinuation of ABL TKI treatment may indeed be possible in CML patients with prolonged CMR. However, no predictive prognostic factors for successful therapy discontinuation have yet been identified.

Recently, Ng *et al.* demonstrated that East Asian CML patients with a common deletion polymorphism in intron 2 of the *BCL2L11* (*BIM*) gene had a lower response to TKIs than to those without the deletion [4]. Augis *et al.* also demonstrated that CML patients with the *BIM* SNP had a lower response to imatinib [5]. We therefore aimed to further our understanding of the predictive biomarkers for molecular relapse and non-relapse after ABL TKI treatment discontinuation. This study was approved by the institutional review board of Tokyo Medical University (no. 1655; approved on January 28, 2011). Patients in CMR receiving TKI treatment were eligible for inclusion in this study. Molecular relapse was defined as a loss of the major molecular response (MMR). Genomic DNA of the patients was obtained from

whole blood using the EZ1 DNA Blood 350 1 kit (Qiagen, Valencia, USA) and was subjected to polymerase chain reaction amplification using primers designed to detect a deletion site (2,903 bp) in intron 2 (deletion polymorphism) and a silent SNP in exon 5 (c465C>T) [6].

Thirty-two CML patients (17 men and 15 women; median age: 57.5 years) were included in this study (Sokal category: low, 24 patients; intermediate, 7 patients; high, 1 patient). Six patients were treated with interferon- α (IFN α) before TKI treatment, and 3 were treated with IFN α after discontinuation of TKI treatment. Five patients (16%) had the *BIM* deletion polymorphism, and 7 patients (22%) had the *BIM* SNP. Furthermore, none of the patients had both *BIM* genetic variants. The median duration from TKI treatment initiation to discontinuation was 80.5 months (range: 22 to 138 months); median duration of CMR before TKI treatment discontinuation was 43.0 months (range: 5 to 97 months). Nine patients showed a loss of MMR, 8 patients relapsed within 6 months, and 1 patient showed a late relapse at 24 months after discontinuation. The cumulative incidence of loss of MMR was estimated as 25.0% at 12 months and 31.3% at 24 months (Figure 1A). The fluctuation of BCR-ABL transcript levels below the MMR threshold (>2 consecutive positive values) was observed in 3.13% of the patients at 24 months after ABL TKI treatment discontinuation.

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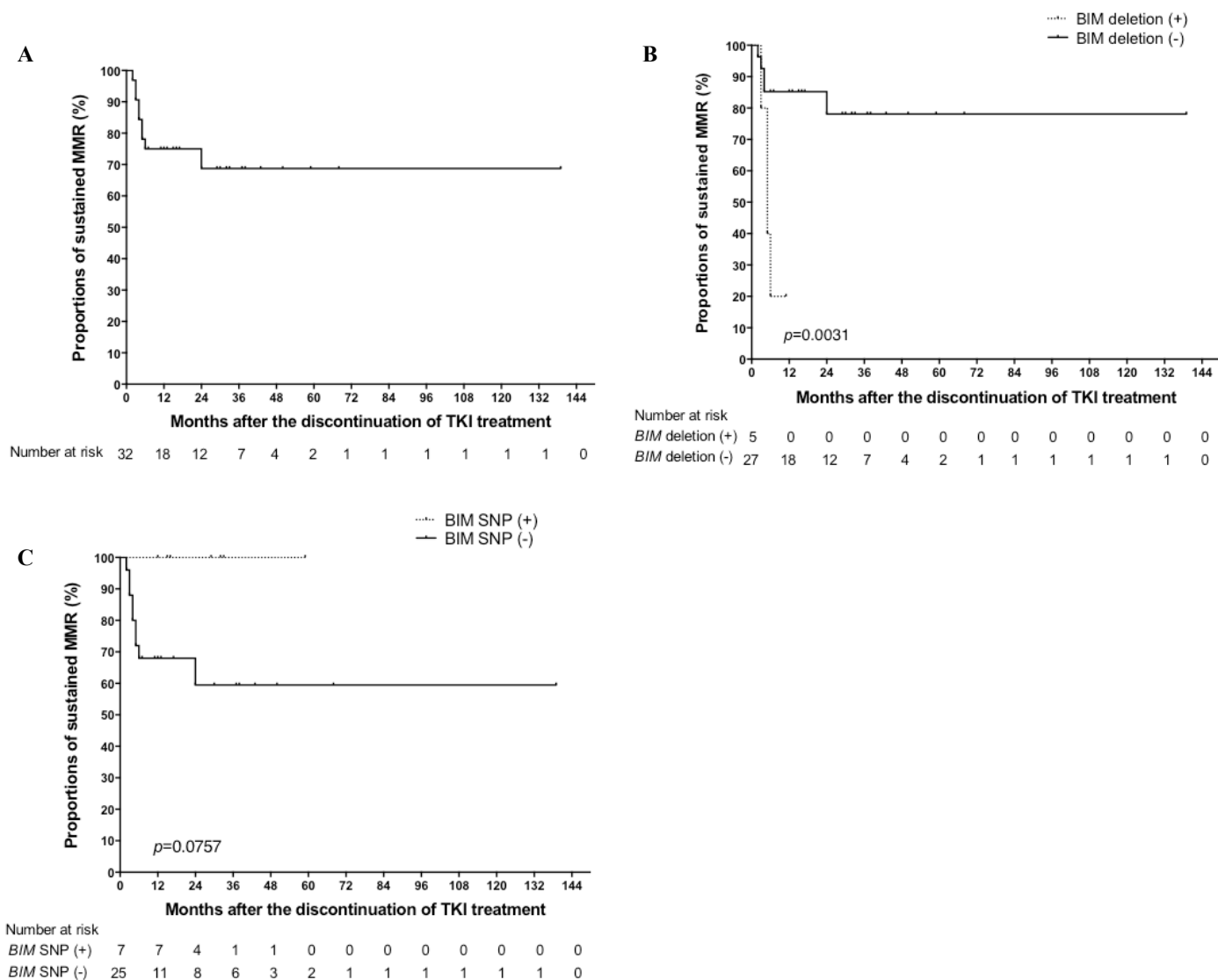


Figure 1. Kaplan-Meier estimates of major molecular remission after discontinuation of tyrosine kinase inhibitor treatment in all 32 patients (A), according to the *BIM* deletion polymorphism (B), and according to the *BIM* SNP (C).

Treatment-free remission was estimated as 75.0% at 12 months and 68.8% at 24 months. The median period of restoration of the second CMR was 6.0 months in re-treated patients. None of the patients died during the follow-up period. TKI-free remission was estimated as 68.8% at 30 months (Figure 1A). A significant difference in the *BIM* deletion polymorphism was only observed between the patients who maintained MMR and those who lost MMR ($p=0.0031$; long-rank test) (Figure 1B). No significant difference was observed in the *BIM* SNP ($p=0.0757$; long-rank test) (Figure 1C), prior IFN α therapy, time to a complete cytogenetic response, time to MMR, and time to CMR between relapsing and non-relapsing patients.

In this study, we found that the *BIM* deletion polymorphism is a better predictor than *BIM* SNP of early molecular relapse after TKI treatment discontinuation in CML patients. However, although the *BIM* deletion polymorphism is found specifically in East Asian patients [4], early molecular relapse was also observed in Caucasian patients. Genetic variations of other BH3-only proteins (for example, PUMA

and NOXA) may also be different between patients of different races.

New biomarkers are becoming available for the identification of patients who are suitable for the future discontinuation of ABL TKI treatment. Here we have shown a specific association between the *BIM* deletion polymorphism and the clinical outcome after ABL TKI treatment discontinuation in patients with long-lasting molecularly undetectable residual disease. We have reached the final stage of establishing the criteria for the discontinuation of ABL TKI treatment in CML patients. We are also beginning to understand the strategies required for the successful discontinuation of ABL TKI treatment. Analysis of the *BIM* deletion polymorphism in CML patients is expected to be useful for predicting their early molecular relapse after the discontinuation of ABL TKI treatment.

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