EDITORIAL

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The role of early molecular predictor in transplant-eligible chronic myelogenous leukemia

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Before the tyrosine kinase inhibitor (TKI) era, allogeneic stem cell transplantation (allo-SCT) was the only curative treatment for chronic myelogenous leukemia (CML). TKI discontinuation studies indicate that the use of TKIs in the treatment of CML can achieve an "operational cure," with lasting freedom from disease progression and disease-related signs and symptoms [1]. However, if the patient has developed a TKI-resistance mutation or cannot tolerate several TKIs, allo-SCT is indicated with a suitable donor. If the patient has advanced CML, allo-SCT is recommended for the blastic phase and accelerated-phase patients who have not achieved an optimal response [2].

In this issue of the *Korean Journal of Internal Medicine*, Lee et al. [3] report that BCR-ABL1 transcripts ($MR^{4.5}$) at 3 months posttransplant predict the long-term outcomes in patients with chronic-phase CML. At 3 months posttransplant, $MR^{4.5}$ was associated with significantly longer event-free survival and showed a trend to lower relapse rates. Their study enrolled 101 patients, of whom 47 were TKI-naïve at the time of transplantation (most were treated during the period before the National Health Insurance Program covered imatinib), while 51 received imatinib as their front-line therapy, and the remaining three patients received one of dasatinib, nilotinib, or bosutinib as front-line therapy. Of the patients for whom a front-line TKI failed, 17 received second-line therapy, of whom eight were treated with a third-line TKI. Although not all enrolled patients were currently indicated for allo-SCT in patients with CML, this study shows the early predictive role of $MR^{4.5}$ at 3 months posttransplant. This is a meaningful finding because it suggests that early intervention with TKI therapy or modulation with immunosuppressive therapy (e.g., donor lymphocyte infusion [DLI] or withdrawal of an immunosuppressive agent) using early molecular monitoring could potentially reduce relapse after allo-SCT in transplant-eligible CML patients.

Previous studies reported that the early detection of BCR-ABL1 transcripts using polymerase chain reaction technology is associated with an increased risk of relapse [4,5]. However, the value of the BCR-ABL1 transcripts expressed in previous studies was not standardized. For molecular monitoring in CML, international efforts have been made to establish recommendations for the interpretation of molecular data. In 2005, experts suggested harmonizing the different methodologies

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for measuring BCR-ABL1 transcripts and using a conversion factor so that individual laboratories can express BCR-ABL1 transcript levels on an internationally agreed scale, that is, an International Scale (IS) [6]. In the work of Lee et al. [3], the value of BCR-ABL1 transcripts was reported on the IS, which is another meaningful feature of this study. The problems with the detection of minimal residual disease in the posttransplant setting in hematological malignancies are the cut-off values and method of standardization for detectable molecular markers. Another problem is when we check the minimal residual disease for detecting early relapse after transplantation. After transplantation, BCR-ABL1 transcripts can be detected or fluctuate at low levels in a minority of patients without obvious progression [7]. Nevertheless, this study suggests a posttransplant checkpoint and cut-off value in CML. Prospective studies must evaluate the frequency of molecular monitoring after transplantation, and validate the checkpoint and cut-off value of BCR-ABL1 transcripts. However, conducting clinical trials will be a challenge due to the lack of transplant-eligible CML patients in the TKI era.

CML is an immunologically sensitive disease following allo-SCT, as proved by the DLI effect in relapsed patients after transplant. TKI therapy after allo-SCT may affect or hinder the immune reconstitution after transplant. A recent study of a small series of patients found that nilotinib prophylaxis after allo-SCT in patients with advanced CML or Philadelphia chromosome-positive acute lymphoblastic leukemia did not jeopardize immune reconstitution or function following transplantation [8]. Further studies must evaluate the role of TKI therapy as prophylactic therapy or preemptive therapy triggered by the detection of minimal residual disease, in the posttransplantation setting in transplant-eligible CML patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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