

Editorial

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Predicting Minimal Residual Disease in Multiple Myeloma: Allelic-Specific Oligonucleotide Real-Time Quantitative PCR or Multi Parametric Flow Cytometry

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Multiple myeloma (MM), an incurable malignant disease is characterized by increased number of clonal plasma cells in the bone marrow. High-dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) and emerging novel therapeutic agents such as bortezomib, thalidomide and lenalidomide achieves very high complete response (CR) up to 50% associated with prolonged survival [1,2]. However, even in those patients disease recurrence/relapse is observed with eventual mortality. This is attributed to the persistent residual tumor cells, known as minimal residual disease (MRD) [3]. The CR has been determined classically by negative serum immunoglobulin immunofixation (IF) [4]. In addition to free light chain assay, highly sensitive techniques are being developed to determine MRD and stringent clinical CR such as allelic-specific oligonucleotide real-time quantitative PCR (ASO-PCR), fluorescent-PCR and multiparametric flow cytometry. Here, the utility of most clinically valuable method to predict MRD in MM patients after autologous or allogeneic stem cell transplantation is discussed, ASO-PCR or multiparametric flow cytometry?

As in other hematologic cancers, detection of Ig heavy chain (IgH) VDJH rearrangements by quantitative ASO-PCR has been generally in use to show disease prognosis in MM patients after stem cell transplantation [3,5]. This is one of the most accurate and sensitive method available. However, one obstacle using ASO-PCR method to predict MRD is somatic hypermutation in VDJH rearrangement which may occur in 60% of MM patients. Somatic hypermutations in VDJH region causes mismatches between primer/probe and target leading to reduced PCR efficiency and occasional false quantification of tumor cells [6,7]. Moreover, ASO-PCR method is a time consuming, complicated and expensive method to use in follow up clinical evaluation. Additionally, the quality of the genomic samples obtained from patients is very important to generate accurate results for MRD. Using other PCR methods such as fluorescent-PCR targeting IgH has not been able to make any improvement to detect prognosis.

Multiparametric flow cytometry is an alternative method for monitoring MRD in MM patients. Multiparameter flow cytometric analysis of peripheral blood and/or bone marrow cells delineates both the number of plasma cells and their phenotypic characteristics as normal and myelomatous plasma cells. Paiva B et al. have recently demonstrated that multiparametric flow cytometry analysis using 4-color (CD38/CD56/CD19/CD45, CD38/CD27/CD45/CD28, and β2-microglobulin/CD81/CD38/CD117) direct immunofluorescence technique was highly sensitive to detect unsustained CR and, to distinguish normal plasma cells and myelomatous plasma cells and in 241 MM patient [8]. Even though multiparametric flow cytometry method is a sensitive, quantitative method, the major disadvantage is higher number of cells required for this method and lower sensitive than ASO-PCR. Conversely, MRD detection using multiparametric flow cytometry provides fast results within a day, compared to ASO-PCR method.

In conclusion, both ASO-PCR and multiparametric flow cytometry methods are able to improve upon our current methods to detect MRD. However, with both advantages and pitfalls of each techniques, a simultaneous response between these two methods is required to eventual adopt of the most sensitive and practical method. Determining MRD by ASO-PCR in bone marrow of patients with MM with a CR after HTD/SCT is an accurate, the most sensitive method to use in routine clinical evaluation. However, multiparametric flow cytometry can be used routinely in clinical evaluation of disease prognosis for being quicker, more distinct in analyzing different phenotypic populations and applicable to high number of patients.

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