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Perspective

Multiple myeloma in Korea: risk stratification and initial treatment

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Introduction

Multiple myeloma (MM) is a heterogenous disease characterized by genomic evolution and mutational profiles with varying clinical course and response to treatment [1, 2]. As of 2004, MM accounted for the second highest medical cost per person in Korea, and the treatment of MM continues to pose a great clinical challenge as both the number of patients and available therapeutic options increase. Therefore, we sought to establish an optimal approach to newly diagnose patients with MM in Korea, with regards to racial differences and inconsistent health-care resource distribution in the country.

Current issues

The introduction of next-generation sequencing (NGS) technology represents an exciting new chapter with respect to multiple aspects in the field of hematology, and MM is not an exception. Because NGS is now rather readily available, it is applied to better characterize the disease at diagnosis and to track minimal residual disease and clonal evolution during subsequent follow-ups [3]. However, we feel that currently in Korea, NGS cannot completely replace fluorescence *in situ* hybridization (FISH) for initial diagnosis. Regarding scientific or technical aspects, as the initiating genetic events in MM primarily involve recurrent translocations at the immunoglobulin heavy chain (IgH) locus on chromosome 14q32, deletions in chromosome 13, and dysregulated expression of cyclin D genes [2], NGS cannot sufficiently detect these widespread structural variations. Moreover, the average turnaround time for NGS results is approximately four weeks. Thus, risk stratification based on the patient's disease biology and subsequent risk-adaptive treatment is virtually impossible using NGS results. Considering the limited first-line treatments, we feel that FISH should remain an integral part in our practice because it is particularly important to identify patients with higher-risk disease for more innovative consolidation and/or maintenance treatment.

The next question was: which FISH panel denotes predictive and prognostic values? Thus far, various groups have proposed different models [4-8]. The International Myeloma Working Group and Mayo group established that FISH testing for t(4;14), t(14;16), and del(17p13) is necessary at initial diagnosis. Meanwhile, the Medical Research Council Myeloma IX trial suggests additional FISH analysis for trisomy 1q and t(14;20), and current NCCN guideline recommends FISH testing for deletion 13, del(17p13), t(4;14), t(11;14), t(14;16), and 1q21 amplification. Based on our experience [9], we recommend testing for del(17p13), t(14;16), t(4;14), 1q21 amplification, and deletion 13 at initial diagnosis. Particularly, we suggest testing for del(17p13) and t(14;16) for their prognostic values and risk stratification, and t(4;14), 1q21 amplification, and deletion 13 for their predictive values for specific therapy. Using one of the biggest real-world practice data set [9], we showed that del(17p13) and t(14;16) are independent adverse predictors

of overall survival. Notably, we sought to understand the different efficacy profiles of therapeutic agents for optimal induction combination strategies. We found that patients with del(17p13) and t(14;16) are less likely to respond to bortezomib, whereas autologous stem cell transplantation (autoSCT) was less effective in those with del(17p13), t(14;16), and 1q21 amplification. Taken together, it seems that FISH abnormalities with predictive impact of bortezomib and autoSCT are the prognostic determinants of overall survival and these predictive values seem universal. However, the predictive marker for lenalidomide appears to be specific to the Korean population. Interestingly, patients with del(13q14) tended to be more refractory to lenalidomide treatment, leading to shorter progression-free survival with lenalidomide (median, 24 mo for del(13q14) negative group vs. 13 mo for del(13q14) positive group; P=0.007) in our study. Finally, based on the improved results observed with bortezomib-based initial therapy, t(4;14) and 1q21 amplification confers little prognostic value. Nonetheless, t(4;14) and 1q21 amplification should be tested for their predictive values of favorable bortezomib response.

The final question is: how do we incorporate cytogenetic information for personalized initial treatment? For autoSCT-eligible patients, the induction treatment is less contentious as the only available option is bortezomib, thalidomide, and dexamethasone (VTD) combination chemotherapy. However, for those with higher-risk diseases, i.e., those with del(17p13) and t(14;16), we suggest initiating a maintenance therapy with newer proteasome inhibitors or immunomodulatory agents for better prognosis. Moreover, these patients should be subjected to more vigilant monitoring as the chances of relapse are higher. For autoSCT-ineligible patients, more variables should be considered. The performance status of the patients is particularly important as frail patients most probably cannot tolerate triple combination therapy, regardless of the biology of their disease. Furthermore, the combined underlying medical conditions, including heart- or kidney-related problems and diabetes or other chronic diseases that put patients at increased risk of severe peripheral neuropathy, should also be considered. Biologically, a bortezomib-containing regimen may be more beneficial for those with t(4;14) and 1q21 amplification and those with possible del(13q14). However, frail patients with higher-risk myeloma may benefit from lenalidomide-based induction therapy. As the use of first-line lenalidomide is expected to increase with its approval, the predictive value of del(13q14) should be corroborated in a larger cohort of patients.

Future perspective

Recent advances in the medical field have enhanced our understanding of MM disease biology and revolutionized the treatment schema. Efforts to identify the different subsets of patients have paid off, and now we have better ideas on how to triage the patients according to risk stratification and deliver risk-adaptive treatment for improved long-term outcomes. However, there are still unmet medical needs, particularly for high-risk myelomas. In Korea, more liberal use of various proteasome inhibitors and combination of immunomodulatory drugs should be warranted for continuous optimization of MM treatment. In addition, with the emergence of monoclonal antibody and many novel agents exhibiting potent activity in MM treatment, collaborative work is vital for the future of MM treatment in Korea.

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Authors' Disclosures of Potential Conflicts of Interest

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

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