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# Guest editorial: basic and clinical updates in multiple myeloma

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Multiple myeloma is a form of B cell malignancy characterized by clonal proliferation of plasma cells within the bone marrow and complex heterogeneous cytogenetic abnormalities. Recent rapid advances in molecular and stem cell biology have been made over the last decade bringing progress in the development of new therapeutic approaches for the treatment of hematological malignancies. Elucidation of the molecular pathogenesis of hematological malignancies has promoted the development of many agents targeting specific molecular pathways, and as a result therapeutic outcomes for these diseases have improved tremendously. As in other hematological malignancies such as leukemia, increasing numbers of cytogenetic and molecular genetic aberrations have been identified in multiple myeloma. These molecular abnormalities provide a better understanding of the biology of multiple myeloma and serve as the basis for targeted therapies. This drug development has been achieved through precise basic research followed by the clinical applications based on the results of large-scale, high-quality clinical trials. The excellent results obtained by molecular targeting through the integration of basic and clinical research are being seen in therapeutic outcomes of multiple myeloma. Novel agents such as thalidomide, lenalidomide, and the proteasome inhibitor bortezomib, which target myeloma cells and their microenvironments, have shown remarkable activity in clinical not only in initial multiple myeloma patients, but also in refractory/relapsed as well, achieving prolonged progression-free and overall survival of the disease.

The present issue of IJH contains four review articles on advances in the study and treatment of multiple myeloma. The authors of these reviews were invited to the 3rd JSH International Symposium on "Molecular-targeting in hematological malignancies: focusing on myeloid malignancy and multiple myeloma" held on May 26 and 27, 2012 in Kawagoe, Saitama, Japan. Eminent basic researchers and clinicians from more than 10 countries working at the forefront of the field participated in this successful meeting, providing a current perspective on molecular targeting in hematological malignancies including multiple myeloma.

The discovery of cancer stem cells in a variety of malignancies is the one of the most exciting topics in the field of cancer biology. As in other hematologic malignancies, the majority of myeloma plasma cells appear mature and quiescent, suggesting possible functional heterogeneity within myeloma cells; myeloma stem or initiating cells have not been identified. The identification of cells responsible for the recurrence of multiple myeloma is of primary importance in designing targeted therapies to definitively cure this disease. Using SCID-hu and SCID-rab mice myeloma models, Dr. Naoki Hosen of Osaka University shows that both $CD38^{++}CD138^{-}$ and $CD38^{++}CD138^{+}$ plasma cells, but not $CD19^{+}$ B cells, demonstrate potent ability to propagate myeloma clones. In addition, he describes the role of the bone marrow microenvironment to support the proliferation of myeloma-initiating plasma cells.

Recent advances in our understanding of the pathogenesis of multiple myeloma have resulted in the development of new agents and increased median survival of patients. Hyperdiploidy and chromosomal translocations focused on

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the immunoglobulin heavy chain variable region contribute to the primary genetic events, which co-operate with secondary events, such as chromosomal deletions and gains, gene mutations, and epigenetic changes in the promoter region of tumor suppressor genes, to produce the malignant phenotype of multiple myeloma. Recent clinical studies have shown that these genetic changes correlate with the clinical outcome of the disease. Drs Marta Chesi and P. Leif Bergsagel of Mayo Clinic Arizona summarize recent advances of genetic alterations of multiple myeloma and relations to the response to new therapeutic agents. In addition, they explain the molecular events of the progression from MGUS (monoclonal gammopathy of undetermined significance) to multiple myeloma.

The third exciting review article, by Drs. Teru Hideshima and Kenneth C. Anderson of Dana-Farber Cancer Institute, focuses on a new therapeutic approach using histone deacetylase (HDAC) inhibitors for multiple myeloma. To further improve clinical outcomes in multiple myeloma, the identification and validation of more new therapeutic agents with less toxicity will be necessary. HDAC inhibitors are a new class of anticancer agents targeting enzymes involved in the epigenetic regulation of gene expression in early clinical development in many malignancies including T cell lymphomas, cutaneous T cell lymphomas, mantle cell lymphomas, and Hodgkin lymphoma. Drs. Hideshima and Anderson describe molecular events underling anti-tumor effects of various classes of HDAC inhibitors and the recent results of clinical trials in multiple myeloma. In terms of anti-myeloma effects, the use of HDAC inhibitors as single agent is modest; therefore, the combination of other agents with HDAC inhibitors may represent a possible future to the treatment of multiple myeloma.

Finally, Drs. Reiko Watanabe, Michihide Tokuhira, and Masahiro Kizaki of Saitama Medical University summarize recent advances in the management of patients with multiple myeloma, based on recent clinical trials using new agents including thalidomide, lenalidomide, proteasome inhibitor bortezomib, and other active agents. This review provides an update on the latest advances in the treatment of multiple myeloma with newly diagnosed and relapsed/refractory patients, the role of autologous transplantation and maintenance therapy. The treatment of multiple myeloma has changed because of the number of possible drug combinations that have been introduced in clinical settings. We need to collect information on the current clinical practice in the management of multiple myeloma and discuss promising strategies for future directions.

I hope that all of the review articles in this issue of IJH will provide our readers with a fuller understanding of recent basic and clinical advances in multiple myeloma and new insights into future directions of the treatment of the disease. While effective treatment of multiple myeloma remains challenging, the survival of multiple myeloma patients has improved in the last decade; to further improve patient care in the future, paradigm shifts will be needed.