

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Utilizing New Biology to Guide Treatment Directions in Myeloma



Gareth J. Morgan, MD, PhD
Professor of Haematology
Department of Haemato-Oncology
The Institute for Cancer Research and
The Royal Marsden NHS Foundation Trust
Surrey, Sutton
United Kingdom

H&O How has the understanding of the biology of multiple myeloma evolved in recent years?

GM Within the last decade, there have been significant advances in our understanding of the biology of multiple myeloma and, subsequently, its treatment approaches. A series of genetic hits in different signaling pathways change the intrinsic biology of the myeloma cell, which leads to a growth and survival benefit. These genetic hits occur in a multistep process, resulting in a number of distinct disease stages, including monoclonal gammopathy of undetermined significance, smoldering myeloma, symptomatic multiple myeloma, and plasma cell leukemia.

H&O How is myeloma classified based on initiation events?

GM It is now recognized that there are 2 broad genetic subtypes of multiple myeloma as defined by chromosome number. The first is hyperdiploid multiple myeloma (48–74 chromosomes), which is characterized by trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21 and a lower prevalence of primary translocations involving the immunoglobulin heavy chain (IgH) locus at 14q32. The second subtype is nonhyperdiploid multiple myeloma (<48 or >75 chromosomes), which is associated with the presence of primary IgH translocations such as t(4;14), t(11;14), and t(14;16). Based on their distribution in the majority of myeloma cells, hyperdiploidy and IgH translocations are believed to represent early or primary genetic events in the multihit disease model of myeloma.

H&O What do such initiation events lead to?

GM These events bring a number of oncogenes (eg, cyclin D1 [CCND1], CCND3, fibroblast growth factor receptor 3 [FGFR3], multiple myeloma SET domain [MMSET], MAF, and MAFB) under the control of the strong IgH enhancers. Further genetic events, such as copy number abnormalities, mutations, and epigenetic modifiers, are required for progression to a malignant phenotype.

H&O Are oncogenes involved?

GM Among some studies, abnormalities of certain oncogenes, such as *c-myc*, appeared to be associated with development early in the course of plasma cell tumors. Further, abnormalities of other oncogenes, such as *N-ras* and *K-ras*, were associated with development after bone marrow relapse. Abnormalities of tumor suppressor genes, such as *TP53*, have been shown to be associated with spread to other organs. Investigations as to whether human leukocyte antigen (HLA)-Cw5 or HLA-Cw2 may play a role in the pathogenesis of multiple myeloma are ongoing.

H&O Can you comment on the clinical implications of these alterations in myeloma therapy?

GM Myeloma prognosis can be linked to both tumor and patient variables. The International Staging System (ISS), which stratifies patients into 3 groups based on serum albumin and $\beta 2$ microglobulin, is the most widely and easily applied prognostic system in myeloma.

Interphase fluorescence in situ hybridization (FISH) is another recent strategy, which considers variations in the genetic and molecular biology of the tumor. An interesting and recent development has been the combined use of ISS and FISH in a prognostic model to provide additional information. For example, high-risk disease can be defined by the presence of multiple adverse FISH lesions combined with ISS II or III and, importantly, patients with a solitary bad lesion in the presence of stage I disease have a neutral prognosis. Thus, there are good data to support the application of this combined ISS and FISH approach to define patient behavior.

H&O Are there any other promising techniques?

GM Gene expression profiling (GEP) provides valuable information on molecular subclass and prognostic risk of multiple myeloma. A number of investigators have used GEP to quantify mRNA levels and have determined a high-risk gene expression profile linked to short survival. However, it should be noted that each of these signatures contains varying numbers of genes (6–70 genes), with few common genes between the signatures. As such, the signatures may be linked to individual treatment protocols. Further work to define the true significance of the genes involved is required before this technique can be used more widely.

H&O What are the biggest remaining challenges?

GM One of the many unanswered questions is determining how to use clinical information to select certain

patient populations for clinical trials. We are beginning to see major improvement in patients with standard-risk disease. However, we are making less progress in the high-risk population. Hopefully, smaller, focused studies will allow us to rapidly find and evaluate new agents for this subgroup.

H&O What do you think the future holds?

GM Going forward, a main goal is to further develop personalized medicine for myeloma. Since one patient's disease might be driven by a different genetic mutation than another patient's, we need to identify what combination of medicine is the most effective for a given genetic driver. The foundation of personalized medicine is about understanding the biology of a particular patient's disease versus calling it a single disease entity, and then targeting the therapy to those drivers.

Suggested Readings

Morgan GJ, Kaiser MF. How to use new biology to guide therapy in multiple myeloma. *Hematology Am Soc Hematol Educ Program*. 2012;2012:342-349.

Walker BA, Wardell CP, Melchor L, et al. Intracлонаl heterogeneity and distinct molecular mechanisms characterize the development of t(4;14) and t(11;14) myeloma. *Blood*. 2012;120:1077-1086.

Boyd KD, Ross FM, Chiecchio L, et al. A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: analysis of patients treated in the MRC Myeloma IX trial. *Leukemia*. 2012;26:349-355.

Kassambara A, Hose D, Moreaux J, et al. Genes with a spike expression are clustered in chromosome (sub)bands and spike (sub)bands have a powerful prognostic value in patients with multiple myeloma. *Haematologica*. 2012;97:622-630.

Anderson K, Lutz C, van Delft FW, et al. Genetic variegation of clonal architecture and propagating cells in leukaemia. *Nature*. 2011;469:356-361.