ADVANCES IN LLM

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

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Use of Genetic Markers in Multiple Myeloma

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H&O In what ways is multiple myeloma a genetically heterogeneous disease?

RF In an editorial written several years ago, I referred to this disease as "multiple and many myelomas." At the genetic level, multiple myeloma is very heterogeneous. Multiple myeloma is a global expansion of clonal plasma cells that become malignant. There are several different subtypes driven by genetic factors, which are well-characterized and reported in similar proportions across different studies. These genetic factors dictate important characteristics, including clinical features, risk, and aggressiveness.

H&O What are the common molecular tests?

RF Classic cytogenetic testing is no longer used. The most common molecular test is fluorescence in situ hybridization (FISH), which must be performed in isolated plasma cells from the bone marrow. It is necessary to isolate the plasma cells because a hemodiluted sample can lead to an incorrect diagnosis. Results from a FISH performed without these methods are useless.

The FISH test is run to identify basic genetic markers for common translocations, as well as for the chromosome 17p deletion, which is a negative prognostic factor. A more expanded approach is used at academic centers, such as Mayo Clinic, where we also test for chromosome 13 and other deletions.

Another strategy is gene expression profiling. This approach also requires the purification of cells. It uses an RNA-expression chip that allows identification of risk factors and genetic subtypes.

H&O How can genetic markers predict for disease type and prognosis?

RF Certain genetic subtypes are associated with a higher propensity for more aggressive disease. Several large clinical trials have shown that genetic markers have a significant influence. Even with the best treatments, patients with certain genetic markers will derive less benefit. For example, despite all the progress made, overall survival for patients with the 17p deletion is less than half that in patients who do not have this abnormality. That is not to say that every patient with the 17p deletion will have a poor prognosis, but the reality is that better treatments are still needed for this population.

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I was fortunate to be part of early efforts that identified the prevalence and clinical importance of immunoglobulin heavy-chain (IgH) translocations in multiple myeloma. This knowledge paved the way for what is now considered the standard approach to risk stratification. We know that some translocations, such as t(4;14) and

t(14;16), carry negative prognostic implications, whereas others, such as t(11;14), are associated with unique clinical features.

A recent effort to quantify risk has combined genetic factors with 2 other markers: lactate dehydrogenase (LDH) and the International Staging System, which is the traditional approach to staging multiple myeloma. The aim of this new strategy, known as the Revised International Staging System, is to more accurately predict prognosis in individual patients (Table).

Table. Entities in the Revised International Staging System for Multiple Myeloma

R-ISS I
• Serum β_2-microglobulin level <3.5 mg/L and serum albumin level ≥3.5 g/dL
• No high-risk chromosomal abnormalities (del[17p], t[4;14], or t[14;16])
• Normal LDH level (less than the upper limit of normal range)
R-ISS III
• Includes ISS stage III (serum β_2-microglobulin level >5.5 mg/L)
• High-risk chromosomal abnormalities or high LDH level
R-ISS II
• Includes all other possible combinations

del, deletion; LDH, lactate dehydrogenase; R-ISS, Revised International Staging System; t, translocation.

Data from Palumbo A et al. *J Clin Oncol*. 2015;33(26):2863-2869.

H&O What genetic markers are used to help select treatment?

RF A patient's genetic subtype can dictate response to various treatments. The understanding is evolving. We recently learned that patients with t(4;14) derive substantial benefit from proteasome inhibitors. In some cases, the identification of particular genetic subtypes has led to new therapies. The best example is the use of venetoclax (Venclexta, AbbVie/Genentech) in patients with t(11;14). In a phase 1 trial presented by Kumar and colleagues at the 2016 American Society of Hematology Annual Meeting, venetoclax was associated with an objective response rate of 21% among 66 patients with relapsed/refractory multiple myeloma. Among the 30 patients with t(11;14), the response rate was 40%. Venetoclax is currently approved by the US Food and Drug Administration for patients with relapsed/refractory chronic lymphocytic leukemia with the 17p deletion. Approval for multiple myeloma appears promising.

Currently, almost all patients receive a proteasome inhibitor for up-front therapy. Patient counseling, in regard to prognosis and outcome, is an important part of treatment selection. Recent progress in the management of myeloma has led some clinicians to now consider it a chronic disease. Management is still challenging, however, among patients who have high-risk genetic markers, classically, t(4;14), t(14:16), and the 17p13 deletion. Survival among these patients is decreased.

Maintenance approaches after stem cell transplant and other treatments are also tailored to the patient's genetic makeup.

H&O When should patients undergo genetic testing?

RF Genetic testing is usually performed at baseline. It might be repeated at certain points throughout the course of the disease if progression is a concern. A patient's basic genetic factors never change, but he or she can acquire secondary abnormalities, such as the 17p deletion; chromosome-1 abnormalities, particularly 1P deletion and 1Q amplification; and MYC abnormalities.

H&O What are some ways to optimize the accuracy of test results?

RF Accurate results of FISH and gene-expression analyses require close attention to the technical aspects of the procedures. At our clinic, we sometimes see patients referred for a second opinion or transplant who were diagnosed incorrectly based on a FISH test that did not isolate plasma cells. These patients have already started treatment, and are therefore ineligible for further testing because there may be too few plasma cells still residing in the bone marrow.

It is also paramount for clinicians to know how to interpret test results and correctly identify the different genetic subtypes of the disease. Confusion about how to categorize subtypes can lead to inaccurate diagnoses. Several guidelines and publications explain the process.

H&O What is the significance of MGUS?

RF Monoclonal gammopathy of undetermined significance (MGUS) refers to a minimal expansion of plasma cells that is a benign, antecedent version of multiple myeloma. MGUS is diagnosed by the presence of monoclonal proteins in the blood. The clonal expansion does not reach a level associated with cancer aggressiveness. It is now known that MGUS always proceeds myeloma, by many years.

MGUS is far more common than multiple myeloma. For patients diagnosed with MGUS, the current standard of care is observation. There is no need for treatment.

H&O What is the role of testing for minimal residual disease?

RF Minimal residual disease describes trace amounts of residual cells in the bone marrow of patients. We are fortunate to have a need for this term. Treatments are becoming so effective that it has become necessary to test for evidence of residual disease after initial therapy, which is usually stem cell transplant. Testing can be performed with flow cytometry or sequencing, which are able to show very low levels of residual cells. Results are used to predict prognosis. There may be other ways to use this measurement, such as for monitoring disease and determining when to discontinue therapy.

H&O Can genetics inform early drug development?

RF Venetoclax is a good example of how genetics can be used in drug development. We still have not identified other genetic factors, such as mutations, that could complement the translocations found in multiple myeloma. In the future, it should be possible to combine new treatments with small-molecule inhibitors that target these genetic factors. Several clinical trials are currently testing this hypothesis.

H&O Has the use of targeted therapies provided insight into the disease process?

RF Yes, and I will go back to venetoclax as an example. Venetoclax was developed for chronic lymphocytic leukemia, but it also works in patients with multiple myeloma and t(11;14). In these patients, myeloma depends on signaling Bcl-2 for antiapoptosis. Therefore, the Bcl-2 signaling becomes the target. This knowledge provides a new basis on which to explore emerging agents.

Another example concerns the immunomodulatory drugs lenalidomide (Revlimid, Celgene) and pomalidomide (Pomalyst, Celgene). My colleagues and I found that these therapies create self-poisoning for cells by inhibiting the mechanisms by which cells dispose of hydrogen peroxide and other byproducts that pollute at high quantities. Results of this study were recently published in *Blood*.

Disclosure

Dr Fonseca is a consultant to Amgen, BMS, Celgene, Takeda, Bayer, Janssen, Novartis, Pharmacyclics, Sanofi, and Merck. He is a member of the Scientific Advisory Board of Adaptive Biotechnologies. Mayo Clinic and Dr Fonseca hold a patent for the prognostication of myeloma via FISH, with annual income of approximately $2000.

Suggested Readings

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