

ADVANCES IN LLM

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

Section Editor: Clara D. Bloomfield, MD

New Molecular Insights in Myelodysplastic and Myeloproliferative Disorders

Peter D. Emanuel, MD
Professor
University of Alabama, Birmingham

H&O Are myelodysplastic and myeloproliferative disorders different diseases?

PE Yes. Myelodysplastic syndromes (MDS) and myeloproliferative disorders (MPD) represent 2 distinct groups of diseases. Both MDS and MPD are myeloid blood cell diseases, while a few subgroups are considered to be a mix of myelodysplastic and myeloproliferative cells, generally these are considered relatively distinct disorders.

H&O What are some of the key features of MDS?

PE One of the main characteristics of MDS that has intrigued investigators for years is its close association to acute myeloid leukemia (AML). As investigators unravel the molecular pathogenesis of AML, relevance to MDS is often noted. Another key feature of MDS is certain chromosomal abnormalities, such as mutations in chromosomes 5, 7, and 8, which are seen fairly frequently. A great deal of research has been devoted to finding specific genetic mutations on these chromosomes that are associated with, and presumably may cause, myelodysplasia. For the most part, although there are some clues about this link, major advances in understanding these mutations have been elusive.

H&O What is known so far about the connection between chromosomal mutations and the development and progression of MDS?

PE We do not really understand much about this connection yet. Do these chromosomal mutations cause MDS? Why do MDS patients who have these specific mutations (eg, on chromosomes 5, 7, and 8) have a worse prognosis? We know that people with these mutations respond less

well to some of the therapies, which are either approved or still being evaluated, but we do not yet know why.

H&O What have any recent studies reported about this association?

PE There have been 2 trials recently performed evaluating lenalidomide (Revlimid, Celgene) in MDS patients, one in MDS patients in general, and another in MDS patients with del5q chromosomal abnormality. In the plenary session at the 2005 annual meeting of the American Society of Clinical Oncology, Dr. Alan List reported on the study of MDS patients with del5q chromosomal abnormality. Patients with the del5q abnormality have disease characterized by severe anemia, thrombocytosis, and an overall better prognosis than other MDS patients. In the study presented by Dr. List, lenalidomide, a thalidomide analog with fewer side effects than its predecessor, improved anemia and the disease in general, both of which were expected outcomes. However, perhaps the most striking result was that this agent caused the cells with the del5q abnormality to basically disappear. This toxic effect on MDS cells was not anticipated, and why it occurred is likely to be the subject of future investigations. Lenalidomide has not yet been approved by the US Food and Drug Administration (FDA) for the treatment of MDS, but may be soon.

Another major development in MDS was the approval by the FDA of azacitidine (Vidaza, Pharmion) in 2004. This agent was the first drug to be specifically approved for the treatment of MDS. Although azacitidine is a chemotherapeutic agent, it has a specific effect on myelodysplastic cells. Now that it is approved, investigators are seeking to further describe its specific effects and which subgroups benefit most from its use.

H&O By what methods is the connection between molecular abnormalities and therapeutic agents studied?

PE These associations are studied through genetic profiling, through clinical trials enrolling patients with specific molecular lesions, and by watching these patients, or cell samples from these patients, along with some further in-depth laboratory studies.

H&O What subgroups comprise MPD?

PE Traditionally, MPD comprises 4 disorders: chronic myeloid leukemia (CML), polycythemia vera (PV), idiopathic myelofibrosis (IMF), and essential thrombocytopenia. In the last few years, the World Health Organization has added some other less common diseases to this list.

H&O How have advancements in understanding the molecular biology of MPD improved therapy over the past few years?

PE Certainly for CML, the last 5–6 years have seen major advances in understanding and improvements in treatment. Imatinib mesylate (Gleevec, Novartis) was the first small-molecule drug developed for any kind of cancer in which the agent was specifically directed at a genetic mutation. This development was the first proof of principle that if the molecular abnormality is known, an effective treatment can be designed. Unfortunately, we are now learning that CML cells can develop resistance to imatinib, just as bacteria can become resistant to antibiotics. A second generation of small-molecule inhibitors is being developed that are, for the most part, more potent than imatinib and largely retain sensitivity/toxicity in CML cells that have developed resistance to imatinib. Two such agents, one developed by Novartis and the other by Bristol-Myers Squibb, are in phase II trials and appear to have promising activity, but final results are awaited.

For PV, IMF, and essential thrombocytopenia, a very significant finding was reported just in the last few months in several journals. Investigators have identified a specific abnormality, called the JAK2 mutation, which is a single point mutation and is present in 80–95% of PV patients, approximately 50% of IMF patients, and approximately 50% of essential thrombocytopenia patients. Reports are now emerging that the JAK2 mutation may also be present in chronic myelomonocytic leukemia and other disorders.

H&O What future investigations are spurred by this finding?

PE Future studies will investigate whether it is possible to develop a specific small-molecule inhibitor against JAK2, just as imatinib targets the BCR/ABL mutation in CML. At the moment, investigators are fairly optimistic that it will be possible to develop such an agent.

Another question that requires investigation is why 2 individuals with the same mutation develop different

disorders. If the JAK2 mutation is present, why does one person develop PV, another essential thrombocytopenia, and another IMF? What other molecular abnormalities may be present to dictate this difference? The identification of this common mutation provides the springboard for a whole new set of investigations to elucidate the mechanisms behind these discrepancies.

H&O How does this finding fit into the bigger picture of hematology research?

PE In terms of the overall theory that identifying molecular abnormalities may play a role in improving treatment outcomes, the identification of the JAK2 mutation is very significant. The currently available therapies for PV, IMF, and essential thrombocytopenia are very nonspecific and are not very satisfactory. No patients are cured without a bone marrow transplantation. Therapies for these disorders have not progressed very far in the last 20 years because we do not know the molecular abnormalities that cause them. Now that an underlying mutation has been identified, the hope is that specific therapies can be developed. While there are not specific treatments targeting the JAK2 mutation yet, the identification of this abnormality is one of the most significant advances in hematology research in the last 10 years.

Suggested Reading

- List AF, Dewald G, Bennett J, et al. Hematologic and cytogenetic (CTG) response to lenalidomide (CC-5013) in patients with transfusion-dependent (TD) myelodysplastic syndrome (MDS) and chromosome 5q31.1 deletion: results of the multicenter MDS-003 study. *Proc Am Soc Clin Oncol*. 2005. Abstract 5.
- List A, Kurtin S, Roe DJ, Buresh A, et al. Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med*. 2005;352(6):549-557.
- Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. *N Engl J Med*. 2005;352(17):1779-1790.
- Baxter EJ, Scott LM, Campbell PJ, et al: Cancer Genome Project. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet*. 2005;365(9464):1054-1061.
- James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. *Nature*. 2005;434(7037):1144-1148.
- Steenma DP, Dewald GW, Lasho TL, et al. The JAK2 V617F activating tyrosine kinase mutation is an infrequent event in both "atypical" myeloproliferative disorders and the myelodysplastic syndrome. *Blood*. 2005 Apr 28; [Epub ahead of print].
- Giagounidis AA, Germing U, Haase S, et al. Clinical, morphological, cytogenetic, and prognostic features of patients with myelodysplastic syndromes and del(5q) including band q31. *Leukemia*. 2004;18(1):113-119.
- Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. *J Clin Oncol*. 2002;20(10):2429-2440.