PROSPECTUS FOR THE FUTURE

Molecular understanding of the pathogenesis of MPNs and acute leukemia is progressing rapidly. It is already promoting development of novel therapeutic approaches that promise to transform the clinical approach to these diseases in the coming years.

Myeloproliferative Disease

The importance of the spectacular success of imatinib as targeted therapy for CML cannot be overstated. As the first successful therapy based on an understanding of pathogenesis, imatinib has become emblematic of the translation of an understanding of disease pathogenesis into tangible innovations in clinical care. Because second- and third-generation TKIs with activity against imatinib-resistant CML are available, SCT is now only rarely offered to patients with CML.

Similarly, the discovery of JAK2 mutations in non-CML myeloproliferative diseases opened new avenues for targeted intervention in diseases for which previous therapy was largely supportive. Treatment with the JAK2 inhibitor, ruxolitinib, has decreased splenomegaly and improved constitutional symptoms in higher-risk myelofibrosis patients independent of JAK2 mutation status. Moreover, provocative results demonstrating that ruxolitinib potentially prolongs overall survival and reduces marrow fibrosis in myelofibrosis patients offer hope that JAK2 inhibitors, like BCR/ABL inhibitors in CML, may eventually alter the natural history of disease.

Acute Leukemia

An understanding of the molecular pathogenesis of acute leukemia has led to important therapeutic advances in the treatment of disease. The discovery of the link between the retinoic acid receptor and the origins of APL provided important insights into the unique sensitivity of this disease to ATRA therapy and paved the road for successful implementation of dual differentiation therapy with ATRA and arsenic. This regimen marks the first time that any acute leukemia can be cured without cytotoxic chemotherapy or SCT.

Oral BCR/ABL kinase inhibitors have become a routine part of the treatment of Philadelphia chromosome–positive ALL. Advances in novel immunotherapeutic approaches that effectively reprogram host T cells to seek out and destroy ALL cells in patients have begun to prove their worth in the clinic and await further clinical validation.

In AML, identification of FLT3 kinase mutations in normal-karyotype AML has led to ongoing clinical trials of targeted inhibitors of this pathway in newly diagnosed and relapsed patients and offer hope for this subset of patients, who historically respond poorly to standard chemotherapy. Similar approaches may soon provide therapeutic entry points into the treatment of other acute leukemias associated with pathognomonic chromosomal translocations and genetic and molecular aberrations. Development of low-dose chemotherapy and reduced intensity SCT strategies has allowed older AML patients the opportunity to live longer and, in some cases, to be cured of their disease.

SUGGESTED READINGS

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