

A New Era in the Treatment of Chronic Myeloid Leukemia

Since the first description of chronic myeloid leukemia (CML) by John Hughes Bennett, MD, and Rudolf Ludwig Karl Virchow, MD, almost 200 years ago, the tremendous advances in the understanding and treatment of this disease have represented important landmarks in the history of medicine, especially given its low incidence (5,000 cases per year in the United States) compared with more common cancers. Fields such as cytogenetics, molecular biology, and targeted therapeutics have grown in parallel with this disease.

The natural history of CML has been dramatically altered since the introduction of tyrosine kinase inhibitors (TKIs). Imatinib, the first molecular-targeted drug incorporated into the treatment of leukemias, produces a high percentage of complete cytogenetic responses. Patients with CML can now expect an excellent long-term survival, often without major side effects. Even though these excellent response rates have placed imatinib as a front-line therapy for CML, they are not equivalent to a cure. In most patients, residual leukemic burden remains, even when not detectable by a sensitive RT-PCR method. Also, in most cases, imatinib interruption is followed by the recurrence of active leukemia, forcing patients into a life-long dependency on the drug.

In spite of this great success, there is still room for improvement. About one-third of front-line patients will not respond to imatinib, and a significant percentage of patients will lose the response over the next years due to resistance and intolerance. The introduction of second-generation TKIs rescues about half of these patients. Nevertheless, a more aggressive upfront therapy might improve overall and progression-free survival as the more rapid debulking could reduce the risk of acquiring resistance mutation while on therapy. A recent trial reported that high-dose therapy with imatinib recently failed to demonstrate its superiority in the primary end point, rate of complete cytogenetic and major molecular responses at 12 months. However, the long-term follow-up of these trials still could demonstrate a benefit in terms of event-free survival since these approaches, as well as the second-generation TKIs as front-line therapy, can achieve a faster “safe haven” in terms of low residual disease. This issue of *Cancer Control* is dedicated to discussing many of these advances and controversies.

The understanding of the molecular biology of CML has allowed for the development of effective molecular-targeted therapies with great success. Still, the presence of minimal residual disease in most of the

patients treated with TKIs remains challenging. In the first article in this issue, Dr Hazlehurst and colleagues review the signaling networks associated with BCR-ABL-dependent transformation. They describe the investigation of BCR-ABL survival and cell growth pathways active in leukemic stem cells and the influence of the bone marrow environment in the persistence of residual cells. Also, the events that take place in the transformation to more aggressive forms of the disease are likely associated with the ability of BCR-ABL to increase the amount of reactive oxygen species that induce DNA damage and impairment of the DNA repair pathways, resulting in a profound genetic instability.

The initial close follow-up of patients with CML under imatinib treatment plays an important part in the successful outcomes in these patients. The achievement of specific milestones under the guidelines of the National Comprehensive Cancer Network and the European LeukemiaNet are important in the identification of patients who do not respond to front-line therapy. In the next article, Dr Mauro tackles this subject with his article on tailoring TKI therapy in CML. In an exhaustive review of the most recent literature, he discusses the monitoring of patients under first-line therapy, the optimal and suboptimal responses, and the prognostic factors and kinase domain mutations that can affect the response to therapy.

The development of resistance is an unfortunate event that places patients with CML at a higher risk of progression if they do not achieve a second cytogenetic response with second-generation TKIs. In about half of the patients, a kinase domain mutation can be detected. In the remaining patients, other mechanisms of resistance have been involved, such as upregulation or downregulation of the drug efflux/influx pumps, BCR-ABL overexpression, and upregulation of LYN kinase. In the following article, Dr Quintás-Cardama and associates offer a thorough overview of the mechanisms of primary and secondary resistance to imatinib in CML.

Second-generation TKIs are now incorporated into our armamentarium of drugs used for imatinib-resistant or -intolerant patients. Two drugs, dasatinib and nilotinib, now approved by the FDA, achieve rates of complete cytogenetic responses in almost half of the patients. Drs McFarland and Wetzstein provide an overview of the use of these two drugs in patients with CML.

For years, bone marrow transplantation has been an important treatment for this disease and remains as the only curative approach. It is known that the graft-

vs-leukemia effect is responsible for the long-term cure of this disease. The success of donor leukocyte infusions also illustrates the importance of this immunologic phenomenon. For these reasons, as well as the persistence of minimal residual disease in most patients, new immunologic interventions are needed. In the next article, my colleagues and I review the more important targets for the development of vaccines and discuss several immunotherapeutic vaccine clinical trials that have been conducted recently. The complex and peculiar interactions between the immune system and the TKIs have opened up the possibility to manipulate the immune system and incorporate new immunotherapeutic approaches with the goal to achieve the cure for this disease.

Allogeneic bone marrow transplant is now reserved for CML patients who fail second-line therapy with TKIs as well as for patients with T315I mutations. Nevertheless, since patient candidates will receive TKIs before and very likely after the transplant, it is important to analyze the outcomes under these new therapies. Drs Fernandez and Kharfan-Dabaja review the current trends in their article on TKIs and allogeneic hematopoietic cell transplantation for CML patients.

This issue of *Cancer Control* summarizes the new approaches being developed in the management of CML. It is likely that the excellent overall survival will continue to improve and, as consequence, the prevalence of this once relatively rare disease will dramatically increase over the next years. But although we have seen advances in our knowledge of CML and its management that have allowed our patients to live longer, continued efforts are needed to address important ongoing issues such as the unknown long-term side effects of these medications, the socioeconomic implications of CML, and the presence of minimal residual disease.

Rounding out this issue, we first include a special report that differs from the majority of articles that we publish. Evidence-based medicine (EBM) is widely taught and used but is criticized by those who believe that it uses a narrow concept of evidence and is in the self-interest of those involved in large-scale clinical trials. Dr Djulbegovic and colleagues examine the validity of EBM using epistemologic (theory of knowledge) techniques and conclude (thank goodness!) that EBM is indeed a valid and constantly changing structure for optimizing clinical practice.

Finally, we have two articles in our "Cancer, Culture and Literacy" feature. In the first, Dr Reyes-Ortiz and colleagues examine why Mexican Americans who have become acculturated in the United States experience a higher rate of cancer than their non-acculturated counterparts. By looking at serum levels of micronutrients in the two groups, they found that, except for selenium and lycopene, acculturation was associated with lower levels of carotenoids and of vitamins E, C, and folate. If

the presence of adequate dietary vitamins is associated with a cancer prevention effect, then this may partially explain the perhaps surprising negative effect of acculturation among Mexican Americans. The second article in this series concerns the racial and ethnic disparities in outcomes of men treated for prostate cancer. Dr Holmes and coworkers questioned if the phenomenon might be related to disparities in the use of androgen suppression in therapy. Using SEER data from a population of 64,000 men with locoregional prostate cancer, they report that while disparities in the use of androgen suppression did indeed exist, this factor was not related to the negative outcomes. Rather, differences in primary therapies used and differences in comorbidity were the true culprits.

We trust that you will enjoy reading this issue of the journal and will benefit from the contributions of our expert authors.

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