Recommendations for the Management of CML in the Era of Second-Generation TKIs

Molecular Pathogenesis and Treatment of Chronic Myelogenous Leukemia

Masahiro Kizaki
Editor

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Editor
Masahiro Kizaki
Department of Hematology, Saitama Medical Center
Saitama Medical University
Kawagoe, Saitama
Japan

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Preface

Advances in treatment of chronic myeloid leukemia (CML) have been made over the past two decades thanks to research that has furthered our understanding of its molecular pathogenesis. CML is a clonal hematopoietic stem cell disorder characterized by the abnormal proliferation of myeloid cell lineages, which progresses through the chronic phase (CP) to the accelerated and blastic phases. CML is caused by the presence of the Philadelphia (Ph) chromosome in hematopoietic stem cells, which arises from the reciprocal translocation of chromosomes 9 and 22, t(9;22)(q34;q11), resulting in the development of the *bcr-abl* chimeric gene. This chimeric gene produces the BCR-ABL fusion protein that has oncogenic activity. The BCR-ABL fusion protein has constitutive tyrosine kinase (TK) activity that is stronger than that of the naïve ABL protein, conferring a proliferative advantage and aberrant differentiation capacity to affected hematopoietic stem cells, resulting in the oncogenic event of leukemia development. Therefore, formation of the *bcr-abl* chimeric gene and its encoded protein is a primary and central event in the molecular pathogenesis of CML.

Until 2000, drug therapy for CML was limited to non-specific cytotoxic drugs such as busulfan and hydroxyurea, and then interferon (IFN)-α was introduced to regress disease activity, which had a survival benefit. Allogeneic hematopoietic stem cell transplantation (allo-SCT) for CML-CP frequently was a curative therapeutic approach for patients with good performance status and an appropriate stem cell donor, but it also was associated with a high incidence of early morbidity and mortality. Understanding of the molecular pathogenesis of CML resulted in rapid development of new therapeutic agents, including various BCR-ABL specific tyrosine kinase inhibitors (TKIs) such as imatinib, nilotinib, and dasatinib. Current clinical guidelines endorse use of any of these three TKIs for initial management of CML-CP. Molecular-targeted therapy with these TKIs was shown to dramatically improve clinical outcomes of CML patients, increasing the 10-year overall survival (OS) from 20 to 80–90 %. As shown in many clinical studies, CML patients treated with TKIs are expected to live for a long period of time. Thus, identification of appropriate surrogate markers for clinical outcome has become important.

Achieving a more complete and faster molecular response is correlated with good clinical outcome; therefore, improving molecular monitoring techniques for minimal residual disease is crucial. Furthermore, management of TKI-resistant CML and development of new TKIs are also important issues. We now have available multiple TKIs for clinical use, including second- and third-generation agents. In this decade, our goals for the treatment of CML are to optimize the quality of life for patients, to establish the most cost-effective treatment, and to deliver the best treatment and monitoring to each patient anywhere in the world. The ultimate goal for any patient is to discontinue use of TKIs—to achieve treatment-free remission and subsequent cure. In other words, future research into treatment of CML will focus on achieving and maintaining complete molecular remission after discontinuation of TKIs.

This book begins with a discussion of recent advances in basic CML research regarding stem cells and the signaling pathways of leukemic cells; continues by describing various clinical aspects of the use of TKIs in daily clinical practice; and concludes with a discussion of future trials aimed at a cure for this disease. I would like to acknowledge the many excellent colleagues who have contributed to each chapter. In addition, I would like to express my appreciation to the staff of Springer Japan, for all of their efforts in bringing this treatise to publication. It is hoped that this book will encourage implementation of further basic and clinical research projects with the goal of solving the remaining intriguing and important clinical problems of CML treatment.

Kawagoe, Japan Masahiro Kizaki, MD, PhD

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