About the Editors

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Foreword

Advances in the treatment of chronic myeloid leukemia

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The prognosis of Philadelphia-positive chronic myeloid leukemia (CML) has been revolutionized since the discovery of the pathogenetic role of BCR-ABL and the invention of tyrosine kinase inhibitors (TKIs). With a follow-up of 8 years, patients had an overall survival of 85%; however, despite those brilliant results obtained, a failure rate of 2–4% per year has been estimated and reported. With second-generation TKIs, dasatinib and nilotinib, approximately 50% of the resistant patients gained a remission with an overall survival over 90% at 2 years. Nowadays, the challenge is preventing resistance leading to progression to advance phases that have little chance of effective treatment. Genomic instability is the drive for progression to accelerated phase (AP) and blast phase (BP): both chromosome aberrations and submicroscopic genetic alterations accumulate during the course of a resistant disease. Different options have been explored in order to reduce failure and progression, such as high doses of imatinib or combination therapy. Both dasatinib and nilotinib were tested as single agents in first-line therapy and compared with imatinib standard dose: the results of Phase II and III trials showed a faster complete cytogenetic response and deeper and faster reduction of molecular burden, with a consequently significant reduction of progression rate. At diagnosis, it is important to stratify patients by risk, because these distinctions have a prognostic relevance and, together with a careful analysis of comorbidities, may suggest a treatment strategy. Appropriate cytogenetic and early molecular monitoring is essential for

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predicting the outcome of patients and deciding on the best therapeutical strategy: either staying on the same treatment or switching to another drug. A growing need for alternative therapies for patients who failed second-generation TKIs emerged. Bosutinib was approved by the US FDA for CP, AP or BP CML with resistance or intolerance to prior TKI, based on Phase II study results in the second-line setting. Ponatinib and omacetaxine have shown promising Phase II activity in patients with the T315I mutation, not previously seen with dasatinib or nilotinib, and in patients failing at least two TKIs. Allogeneic hematopoietic stem cell transplantation is a curative treatment in CML utilizing the antileukemic effects of conditioning, in combination with graft-verus-leukemia, and it is indicated in patients intolerant or unresponsive to TKIs, or in patients who are in AP or BP. Another objective for CML patients in 2013 is the discontinuation of the treatment. Second-generation TKIs in the first-line setting seem to achieve deeper rates of molecular response, necessary for discontinuation. Whether 'cure' of CML can be achieved without allogeneic hematopoietic stem cell transplantation or continued TKI therapy is still an open question. Therapy withdrawal in patients in sustained CMR on imatinib led to relapse in approximately 60% of cases. It is unclear why some patients do not relapse. Several mechanisms may contribute to further decrease and/or keep under immunological control of a residual leukemic burden. At present, TKI interruption cannot be recommended outside the setting of a clinical trial.

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