Abstract. Despite the excellent clinical results with imatinib in chronic myeloid leukemia, most patients have minimal residual disease and others will develop resistance and may eventually progress. Thus there is a need for developing approaches to overcome and prevent resistance to imatinib. The “second generation” of more potent tyrosine kinase inhibitors have shown significant activity in the laboratory and in the clinic. However, there is considerable interest in developing agents that may act on different pathways that could either be combined with these inhibitors to better overcome and eventually prevent the development of resistance, to deal with mechanisms of resistance common to all inhibitors, or to deal with the problem of residual disease, that could be mediated by a stem cell insensitive to tyrosine kinase inhibitors. To this effect, many agents have been developed and have already entered the clinical arena, such as hypomethylating agents, farnesyl transferase inhibitors, and homoharringtonine, with promising preclinical and clinical results. Others may have been tested only at a preclinical level but have shown important ac-
tivity. In addition, the use of immune modulation, for example, in the form of “vaccines,” is evolving as a major strategy to achieve eradication of minimal residual disease. This chapter will discuss some of the different agents currently under development, with particular attention to those already in clinical trials. The challenge for the future is to incorporate them into effective strategies that can eliminate the disease and cure all patients with chronic myeloid leukemia.

10.1 Introduction

The hybrid gene BCR-ABL resulting from the t(9;22) is crucial in the pathogenesis of CML (Daley et al. 1990; Faderl et al. 1999; Sawyers 1999). BCR-ABL encodes an 8.5-kb chimeric mRNA that translates into a 210-kDa protein with constitutively activated tyrosine kinase. Importantly, the p210bcR-ABL protein is distinctly restricted to CML cells, thus making it an optimal target for targeted therapeutic approaches. Imatinib mesylate (Gleevec) has ushered in the era of molecular therapeutics in CML and has become the standard in CML treatment due to its potent and selective Bcr-Abl tyrosine kinase inhibitory activity (Kantarjian et al. 2002; O’Brien et al. 2003; Talpaz et al. 2002). Eighty to 90% of patients with CML in early chronic phase achieve a complete cytogenetic response with imatinib (Kantarjian et al. 2002; O’Brien et al. 2003). These unprecedented results notwithstanding, imatinib may not eliminate all detectable BCR-ABL-positive cells in a substantial proportion of patients (Hughes et al. 2003); this may eventually lead to the development of resistance to imatinib and transformation to the advanced stages of the disease (Cortes et al. 2005). Mutations in the BCR-ABL tyrosine kinase domain, BCR-ABL overexpression or amplification, and overexpression of Src-related kinases are some of the mechanisms invoked in imatinib resistance (Branford et al. 2004; Corbin et al. 2003; Donato et al. 2004; Griswold et al. 2004). BCR-ABL kinase domain mutations can be demonstrated in 30 to 90% of patients who become resistant to imatinib. More than 30 different point mutations have been reported with different potential for preventing inhibition by imatinib (Corbin et al. 2003). In addition, patients in major molecular responses in whom therapy with imatinib is interrupted experience recurrence of their disease, providing further evidence that residual disease is still present. This may be due to persistence of a subset of quiescent and primitive BCR-ABL-positive cells. The persistence of this innate imatinib-insensitive cell population could eventually lead to development of clinical relapse and resistance to imatinib. Thus, current efforts in CML therapy are directed towards development of new strategies to overcome the mechanisms of imatinib failure, aiming at complete elimination of leukemic progenitor cells. Herein, we provide a review of the therapy for CML, with emphasis on innovative strategies. A family of new, more potent tyrosine kinase inhibitors, some of them with the dual ability to inhibit Src, have shown significant activity in preclinical and clinical studies. These agents are described elsewhere in this book. Here we focus on agents directed at other targets that have shown promise in preclinical studies and some of them also in clinical trials.

10.2 Farnesyl Transferase Inhibitors

Ras gene mutations are commonly encountered in leukemia. Once activated, Ras can stimulate signal pathways that ultimately promote cellular proliferation (Vojtek and Der 1998). In CML, downstream activation of Ras is one of the main events resulting from the Bcr-Abl tyrosine kinase activity. Ras is initially synthesized in the cytoplasm as an inactive protein and later attaches to the membrane. This latter step is critical in Ras function and is accomplished through a posttranslational reaction termed prenylation. During prenylation a 15-carbon isoprenyl (farnesyl) group is attached to the Ras C-terminal cysteine by an enzyme called farnesyltransferase (Ftase) and to a lesser extent by geranylgeranyl-protein transferases (GGPTases) (Beaupre and Kurzrock 1999). Inhibition of the enzymes responsible for prenylation has been sought as a means of inhibiting Ras. In CML, inhibition of Ras may suppress cellular growth in Bcr-Abl-positive hematopoietic cells. Although the development of Ftase inhibitors (FTIs) was initially designed to block Ras signaling, it has become evident that the biologic and clinical effects of FTIs have little to do with inhibition of Ras. Instead, other regulatory proteins equally dependent on prenylation may be more relevant for this effect. Examples of the latter include RhoB, Rab, and the centromeric proteins CENP-E and CENP-F.

The potential for activity of FTIs in CML was first demonstrated in Bcr-Abl-positive cell lines. Lonafarnib (SCH66336), a nonpeptidomimetic FTI, abrogated in a dose-dependent fashion colony formation and prolifera-