TYROSINE KINASE INHIBITORS IN CHRONIC MYELOID LEUKEMIA

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1.1 Introduction

The BCR-ABL protein tyrosine kinase is the product of a chimeric gene produced by the Philadephia (Ph) chromosome. Initially identified in 1960, the Ph chromosome results from a reciprocal translocation between the long arms of chromosomes 9 and 22. Chronic myeloid leukemia (CML) is a myeloproliferaive disorder that results from this acquired mutation affecting hemapoietic stem cells. Imatinib, also known as Gleevac, developed by Novartis, is a specific inhibitor of BCR-ABL tyrosine kinase. If untreated CML inevitably progresses to more aggressive accelerated and blast phases. Once in blast phase the median survival of patients is less than 6 months. Imatinib has substantial activity in the chronic phase, as well as significant activity in the accelerated phase and the blast crises phase of CML [1, 2].

1.2 Mechanism of Action and Development

There is a family of enzymes called protein tyrosine kinases that bind adenosine triphosphate (ATP) and catalyse the transfer of the γ-phosphate to the hydroxyl group of a tyrosine residue on a protein. In a signal transduction cascade these phosphorylated sites can then serve as binding sites for phosphorylation of other substrates. The kinases themselves are usually activated either by interaction of a ligand with a receptor located within the extracellular domain of the kinase or, alternatively, as part of an intracellular signaling pathway. The human genome encodes upto 800 serine/threonine and tyrosine protein kinases, all of which bind ATP in a highly conserved fashion within their catalytic domains. Molecules collectively referred to as kinase inhibitors that are currently available possess an inhibitory profile whereby they inhibit the target kinase with relative selectivity toward other often closely related kinases to give an acceptable side effect profile [3].

In vitro and animal studies have established that BCR-ABL alone is sufficient to cause CML, and mutational analysis has established that tyrosine kinase activity of the protein is required for its oncogenic activity [4]. The ABL gene encodes the tightly regulated nonreceptor protein tyrosine kinase cytosolic ABL (cAbl), which plays a fundamental role in regulating cell proliferation, adherence, and apoptosis [5]. In contrast, the BCR-ABL fusion gene encodes a constitutively activated kinase. This transformation results in hemopoeitic stem cells to exhibit deregulated clonal proliferation, reduced adherence to bone marrow stroma, and reduced apoptotic response to disruption in cellular genomic integrity. As a result immature cells of the myeloid lineage are released into the blood in various stages of maturation as well as populate the reticuloendothelial system organs such as the liver and the spleen [6, 7].

This has rendered BCR-ABL an attractive target for drug intervention in CML. Unlike membrane-bound receptor tyrosine kinases, BCR-ABL is a cytoplasmic kinase. It is constitutively active and does not depend

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