Tyrosine Kinase Inhibitor Treatment for Newly Diagnosed Chronic Myeloid Leukemia

Jerald P. Radich, MD[a,*], Michael J. Mauro, MD[b]

KEYWORDS

- Chronic myeloid leukemia • Tyrosine kinase Inhibitor • Imatinib • BCR-ABL
- Molecular response

KEY POINTS

- Tyrosine kinase inhibitor (TKI) therapy has radically changed the natural history of chronic myeloid leukemia.
- "First-line" therapy with imatinib or the second-generation TKIs produce similar long-term survival results, with different early and "late" toxicities.
- Progression to advanced phase disease appears to be less frequent in patients treated with second-generation TKIs.
- Molecular monitoring of BCR-ABL is a powerful tool to document treatment response.
- Some patients with sustained deep molecular response can undergo TKI discontinuation under close monitoring and not relapse.

INTRODUCTION: A SHORT HISTORY OF THE DEVELOPMENT OF TYROSINE KINASE INHIBITOR THERAPY

Chronic myeloid leukemia (CML) is a myeloproliferative disorder marked by the increased proliferation of granulocytic cell lineage cells that retain the ability to differentiate. Nowell and Hungerford in 1960[1] described a small chromosome in metaphase preparations of marrow from patients with CML. This abnormal chromosome was dubbed the Philadelphia chromosome (the location of the investigators parent institution) and was later demonstrated to be the result of a translocation between chromosomes 9 and 22 [t(9;22)(q34;q11)].[2] The translocation results in the production of an abnormal BCR-ABL fusion protein, which is a constitutively

[a] Clinical Research Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, D4-100, Seattle, WA 98104, USA; [b] Myeloproliferative Neoplasms Program, Leukemia Section, Memorial Sloan Kettering Cancer Center, 1275 York Avenue (Between 67th and 68th street), New York, NY 10065, USA
* Corresponding author.
E-mail address: jradich@fredhutch.org

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active cytoplasmic tyrosine kinase.[3,4] The Ph chromosome is found in myeloid, erythroid, megakaryocytic and B-lymphoid cells, suggesting that the original genetic lesion occurs in a stem cell.

The normal ABL protein is a nonreceptor tyrosine kinase with important roles in signal transduction and the regulation of cell growth.[5] The BCR-ABL protein, unlike normal ABL, is constitutively active and has increased kinase activity, leading to continuous activation of several cytoplasmic and nuclear signal transduction pathways including STAT, RAS, JUN, MYC, and phosphatidylinositol-3 kinase.[6] In experimental mouse systems, BCR-ABL causes myeloproliferative diseases similar to human CML, although chronic phase has been difficult to simulate.[7–9] In vitro studies show that BCR-ABL expression allows cells to become cytokine independent, protects them from apoptotic responses to DNA damage, and increases adhesion of hematopoietic cells to extracellular matrix proteins.[10–12]

The advent of tyrosine kinase inhibitor (TKI) therapy has fundamentally changed the approach of treating CML. The first TKI against BCR-ABL was imatinib mesylate (also known as STI571; Gleevec/Glivec). Imatinib is a small molecule inhibitor of several protein tyrosine kinases including the ABL tyrosine kinase, C-KIT, and PDGF. Imatinib was found to specifically inhibit or kill proliferating myeloid cell lines containing BCR-ABL *without effect on normal cells*.[13] This observation quickly led to a phase 1 trial in 1998 testing imatinib in patients with chronic phase CML who had failed interferon (IFN) -based therapy.[14] Of 54 patients who received oral doses of imatinib of 300 mg/d or more, a remarkable (at the time, *unbelievable*) 53 had a complete hematologic response, and cytogenetic responses were seen in 54% of cases. A second study of 58 patients with myeloid or lymphoid blast crisis CML (or Ph-positive ALL) showed partial/complete response in 60% to 70% of patients.[15] The toxicity profile of imatinib in these phase 1 studies was very encouraging, lying between the relatively benign hydroxyurea and the more problematic IFN. Nausea, edema, and muscle cramps occurred in roughly 50% of patients with diarrhea, vomiting, rash, and headache seen in about a third of cases.

Phase 1 results were then confirmed in phase 2 studies, and in 2001 imatinib was approved in the United States for chronic phase CML resistant to IFN as well as CML in accelerated or blast phases. Next came the substantial (N = 1106 patients) IRIS phase 3 study comparing imatinib to IFN plus cytarabine for newly diagnosed chronic phase CML.[16] At 12 months, complete cytogenetic remission (CCyR) was seen in ~70% of the imatinib-treated patients versus 7% with IFN and Ara-C therapy, and progression was seen in only 1.4% of the imatinib group compared with 10.3% of the IFN cases. Moreover, therapy crossovers for drug toxicity occurred in a mere 1% of imatinib-treated patients compared with 19% of IFN-treated patients. The study was closed early based on the outstanding efficacy advantage of imatinib. The superb short-term results were confirmed by a 5-year follow-up, where the overall survival of imatinib-treated patients was 89%, with progression to advanced phase disease in 7%.[17] Remarkably, nearly 70% of patients remained in CCyR at the 5-year mark.

Thus, the shape of CML was changed forever.

TKI therapy has revolutionized the treatment of CML, giving patients with chronic phase disease a near normal age-adjusted lifespan.[18] Given this success, CML will become a very prevalent oncologic diagnosis in the future, despite its relatively low incidence of roughly 5000 cases per year in the United States. Estimates in the United States are for a steady-state prevalence of CML of roughly 200,000 individuals rather than the pre-TKI level of ~25,000 individuals. Thus, it is important for the general oncologist to recognize and appreciate the special issues in diagnosing and caring for patients with CML in order to optimize their short- and long-term treatment