ABSTRACT

CML is a haematopoietic stem cell disease, which characterized by a reciprocal translocation between chromosome 9 and 22, resulting in formation of the Philadelphia chromosome (ph chromosome). Tyrosine kinase inhibitors have proven particularly efficient in the treatment of CML. Nevertheless, MTTS can inhibit major pathways in normal or cancerous cell leading to unexpected off-target side effects, morbidity, reduced drug doses, or even drug cessation. Hypertension is one of the complications of TKIs, treatment with TKIs that target vascular endothelial growth factor (VEGF) is associated with hypertension that can be life-threatening and cause damage to eyes, brain, or kidneys.

Left ventricular systolic dysfunction and heart failure is a second complication. While, diagnosis of heart failure based on clinical and physical examination remains difficult in daily clinical practice. Q-T interval prolongation has garnered attention because of its risk of malignant arrhythmia with torsade de pointe sudden cardiac death.

Keword

CML - card

INTRODUCTION

Chronic myelogenous leukaemia accounts for 15% of adult leukaemias. The median age of disease onset is 67 years. However, CML occurs in all age groups (SEER statistics) ***(Jemale et al., 2010).***

CML is a haematopoietic stem cell disease, which characterized by a reciprocal translocation between chromosome 9 and 22, resulting in formation of the Philadelphia chromosome (ph chromosome). This translocation t(9:22) results in the head to tail fusion of the break point cluster region (BCR) gene on chromosome 22 at band q11 and the Abelson murine leukaemia (ABL) located on chromosome 9 at band 34 ***(Faderl et al., 1999)***.

The product (BCR-ABL) is believed to play a central role in the initial development of CML.

CML occurs in three different phases (chronic, accelerated and blast phase) and is usually diagnosed in the chronic phase. The bulk of genetic changes in progression occur in the transition from chronic phase to accelerated one ***(Radich et al., 2006)***.

Untreated chronic phase CML (CP-CML) will eventually progress to advanced phase CML in3-4 yearsThe activation of beta-catenin-signaling pathway in CML granulocyte-macrophage progenitors (which enhances the self-renewal

activity and leukaemic potential of these cells) may also be a key pathobiologic event in evolution of blast phase CML ***(Jamieson et al., 2004)***.

Over the last two decades, considerable progress has been achieved in the management of cancer with the introduction and use of molecular targeted therapies (MTTs).

Of MTTs tyrosine kinase inhibitors have proven particularly efficient in the treatment of CML. Nevertheless, MTTS can inhibit major pathways in normal or cancerous cell leading to unexpected off-target side effects, morbidity, reduced drug doses, or even drug cessation ***(Krause and VanEtten, 2005)***

Imatinib mesylate is considered a selective inhibitor of the BCR-ABL tyrosine kinase ***(Jabbour et al., 2007)***. Newly diagnosed patients were evaluated in the IRIS (International Randomized Study of Interferon and ST1571) trial. In this trial, 1106 patients were randomized to receive initial therapy with either 400mg of daily imatinib or interferon-alpha plus low dose cytarabine. The major cytogenetic response (MCyR) at18 months was87.1% in imatinib group versus 43.7% in the control group ***(O'Brien et al., 2003).***

In December 2002, FDA approved imatinib for the first line treatment of patients with CML based on the results of IRIS study.

Dasatinib is a potent, orally available ABL kinase inhibitor, similar to imatinib, but with the added advantage in that it can bind to both active and inactive conformation of ABL kinase domain. As a result, dasatinib is active against nearly all imatinib-resistant BCR-ABL mutations ***(Shah et al., 2004)***.

Nilotinib is a new orally available, highly selective inhibitor of BCR-ABL tyrosine kinase (20-50 times more potent in imatinib-resistant cell lines, and 3-7 more potent in imatinib-sensitive cell lines) ***(Kantarjian et al., 2007)***. So, it is used as first line treatment of CML.

Hypertension is one of the complications of TKIs, treatment with TKIs that target vascular endothelial growth factor (VEGF) is associated with hypertension that can be life-threatening and cause damage to eyes, brain, or kidneys.

Left ventricular systolic dysfunction and heart failure is a second complication. While, diagnosis of heart failure based on clinical and physical examination remains difficult in daily clinical practice ***(Fonseca, 2006)***.

Moreover, diagnosis of heart failure based on presence of dyspnea, fatigue, and peripheral oedema.

Echocardiography, which is a non-invasive real-time imaging techniques, is considered as the single most useful diagnostic test in the evaluation of patients with heart failure, according to ACC/AHA guidelines ***(Jessup et al., 2009)***.

Q-T interval prolongation has garnered attention because of its risk of malignant arrhythmia with torsade de pointe sudden cardiac death ***(Haverkamp et al., 2000)***.

In a phase I study, 119 patients with imatinib resistant CML received nilotinib orally at doses varying from50-1200mg once daily, QTc interval increased by 5-15 ms In phase II studies, QTc prolongation >60ms was reported in 1.9%, and 2.5% patients with chronic and accelerated-phase CML respectively ***(Hazarika et al., 2008).***

AIM OF THE WORK

To evaluate cardiovascular side effects of treatment with tyrosine kinase inhibitors in patients with CML in relation to dose, duration of treatment and the effect of TKIs on previously existing cardiac disease.

Chapter 1

CHRONIC MYELOGENOUS LEUKEMIA

DEFINITION AND HISTORY

Chronic myelogenous leukemia (CML) is a pluripotential stem cell disease characterized by anaemia, extreme blood granulocytosis and granulocytic immaturity, basophilia, often thrombocytosis, and splenomegaly. The hematopoietic cells contain a reciprocal translocation between chromosomes 9 and 22 in more than 95 percent of patients, which leads to an overtly foreshortened long arm of one of the chromosome pair 22 (i.e. 22, 22q-) referred to as the Philadelphia (Ph) chromosome ***(Nowell et al., 1960)***. A rearrangement of the breakpoint cluster gene on the long arm of chromosome 22 defines this form of CML and is present even in the 10 percent of patients without an overt 22q abnormality by Giemsa banding. The natural history of the disease is to undergo clonal evolution into an accelerated phase and/or a rapidly progressive phase resembling acute leukemia, which is refractory to therapy.

EPIDEMIOLOGY

CML, accounts for approximate 15 percent of all cases of leukemia, or approximately 5000 new cases per year in the

United States. The age-adjusted incidence rate in the United States is approximately 2.0 per 100,000 persons for men and approximately 1.1 per 100,000 persons for women. The incidence around the world varies by a factor of approximately twofold ***(Redaelli et al., 2004)***. The lowest incidence is in Sweden and China approximately 0.7 per 100,000 persons, and the highest incidence is in Switzerland and the United States approximately 1.5 per 100,000 persons ***(Hemminki et al., 2002)***. The age-specific incidence rate for CML in the United States increases logarithmically with age, from approximately 0.2 per 100,000 persons younger than 20 years to a rate of approximately 10.0 per 100,000 octogenarians per year. Although CML, occurs in children and adolescents, less than 10 percent of all cases occur in subjects between 1 and 20 years old. CML, represents approximately 3 percent of all childhood leukemias. Multiple occurrences of CML in families are rare. There is no concordance of the disease between identical twins. Analytical epidemiologic evidence for a familial predisposition in CML was not found in a Swedish database, ***(Hemminki et al., 2002)***.

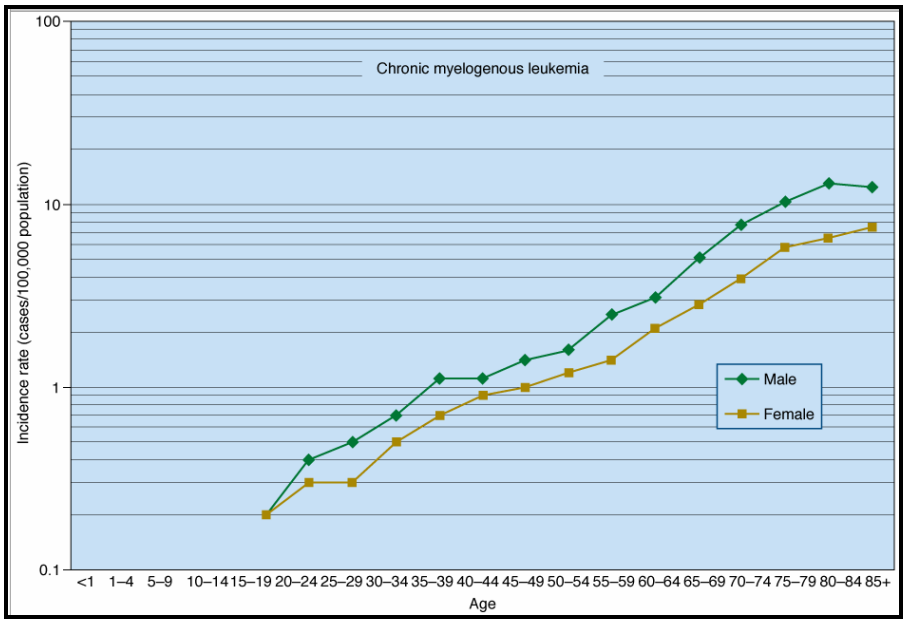

Figure (1): Incidece of chronic mylogenous by age. Note the exponential increase in incidence with age from about teenagers to octogenarians, Rare cases in younger children but too few generate an incidence rate.

ETIOLOGY AND PATHOGENESIS

ENVIRONMENTAL LEUKEMOGENS

Exposure to very high doses of ionizing radiation can increase the occurrence of CML above the expected frequency in comparable populations. Three major populations-the Japanese exposed to the radiation released by the atomic bomb detonations at Nagasaki and Hiroshima, ***(Ichimaru et al., 1971)***, British patients with ankylosing spondylitis treated with spine irradiation, ***(Court Brown et al., 1959, 1960)***, and women with uterine cervical carcinoma who received radiation therapy, ***(Boice et al., 1985)***. Chemical leukemogens, such as

benzene and alkylating agents, are not causative agents of CML, although they are well established to produce a dose-dependent increase in acute myelogenous leukemia ***(Lichtman, 2008)***.

- **PROGENITOR CELL CHARACTERISTIS**

- **Progenitor Cell Dysfunction**

The leukemic transformation resulting from the BCR-ABL fusion oncogene is maintained by a relatively small number of BCR-ABL stem cells that favor differentiation over self-renewal ***(Holyoake et al., 2002)***. This predisposition to differentiation and progenitor cell expansion is mediated by an auto-crine interleukin (IL)-3-granulocyte colony- stimulating factor (G-CSF) loop ***(Holyoake et al., 2002)***. The earliest progenitors have the capacity to undergo marked expansion of erythroid, granulocytic, and megakaryocytic cell popu-lations, and have a decreased sensitivity to regulation ***(Eaves et al., 1998)***. BCR-ABL reduces growth factor dependence of progenitor cells.

Erythroid progenitors are expanded, erythroid precursor maturation is blocked at the basophilic erythroblast stage, and the extent of erythropoiesis is inversely proportional to the total white cell count ***(Sjogren et al., 1974)***.

- **EFFECTS OF BCR-ABL ON CELL ADHESION**

Primitive progenitors and blast colony-forming cells from patients with CML have decreased adherence to marrow stromal cells ***(Dowding et al., 1991)***. This defect is normalized if stromal cells are treated with interferon alpha. As a result, BCR-ABL-negative progenitors are enriched in the adherent fraction of circulating CD34+ cells in chronic phase CML patients. The most primitive BCR-ABL-positive cells in the blood of patients with CML differ from their normal counterparts. They are increased in frequency and are activated, such that signals that block cell mitosis are bypassed.

Ph-chromosome-positive colony-forming cells adhere less to fibronectin (and to marrow stroma) than do their normal counterparts. Adhesion is fostered as a result of restoration of cooperation between activated β_1 integrins and the altered epitopes of CD44 ***(Bhatia et al., 1998)***. BCR-ABL-induced defects in integrin function may underlie the abnormal circulation and proliferation of progenitors ***(Deininger et al., 2000)*** because growth signaling can occur through the fibronectin receptor. IFN-alpha restores normal integrin-mediated inhibition of hematopoietic progenitor proliferation by the marrow microenvironment. There are conflicting data regarding the effects of tyrosine kinase inhibitor effects on adhesion of CML cells to stroma ***(Wertheim et al., 2002)***.

BCR-ABL-encoded fusion protein $p210^{BCR-ABL}$ binds to actin, and several cytoskeletal proteins are thereby phosphorylated. The $p210^{BCR-ABL}$ interacts with actin filaments through an actin-binding domain. BCR-ABL transfection is associated with increased spontaneous motility, membrane ruffling, formation of long actin extensions (filopodia), and accelerated rate of protrusion and retraction of pseudopodia on fibronectin-coated surfaces. In normal cells exposed to IL-3, paxillin tyrosine residues are phosphorylated. In cells transformed by $p210^{BCR-ABL}$ the tyrosines of paxillin, vinculin, $p125^{FAK}$, talin, and tensin are constitutively phosphorylated. Pseudopodia enriched in focal adhesion proteins ***(Salgia et al., 1995)*** are present in cells expressing $p210^{BCR-ABL}$.

The sum of evidence suggests that defects in adhesion (contact and inchoring) of CML primitive cells remove them from their controlling signals normally received from microenviromental cells via cytokine messages. These signals retain the balance among cell survival, cell death, cell proliferation and cell differentiation. Inappropriate phosphorylation of cytoskeletal proteins, possibly independent of tyrosine kinase, is thought to be the key factor in disturbed integrin function of CML cells.

- **MOLECULAR PATHOLOGY**

Ph Chromosome

The genetic disturbance became evident with the knowledge that CML was derived from a primitive cell containing a 22q- abnormality. Using quinacrine (Q) and Giemsa (G) bandig, Rowley ***(Rowley, 1973)*** reported that the material missing from chromosome 22 was not lost (deleted) from the cell, but was translocated to the distal portion of the long arm of chromosome 9. The amount of material translocated to chromosome 9 was approximately equivalent to that lost from 22, and the translocation was predicted to be balanced. Moreover, the breaks were localized to band 34 on the long arm of 9 and band 11 on the long arm of 22. Therefore, the classic Ph chromosome is t(9; 22) (q34; q11), abbreviated t (Ph) (Fig. 2). The Ph chromosome can develop on either the maternal or the paternal member of the pair.

Mutation of ABL and BCR Genes

Mutations of the ABL gene on chromosome 9 and of the BCR gene on chromosome 22 are central to the development of CML (Fig. 3), ***(Melo et al., 2004)***.

Human cellular homologue ABL of the transforming sequence of the Abelson marine leukemia virus was localized

to human chromosome 9. ABL was shown to be on the segment of chromosome 9 that is translocated to chromosome 22 by demonstrating reaction to hybridization probes for ABL only in somatic cell hybrids of human CML cells containing 22q- but not those containing 9q+. The ABL gene is rearranged and amplified in cell lines from patients with CML lines and fresh isolates of CML cells contain an abnormal, elongated 8-kb RNA transcript**,** which is transcribed from the new chimeric gene produced by the fusion of the 5' portion of the BCR gene left on chromosome 22 with the 3' portion of the ABL gene translocated from chromosome 9. The fusion messenger RNA (mRNA) leads to the translation of a unique tyrosine phosphoprotein kinase of 210 kDa ($P210^{BCR-ABL}$) which can phosphorylate residues on cellular proteins similar to the action of the v-abl protein product. The anomalous tyrosine kinase is difficult to identify in chronic phase cells because of inhibitors in granulocytes.

The ABL locus contains at least two alleles, one having a 500-bp deletion ***(Jonas et al., 1991)***. In normal cells, the ABL proto-oncogene codes for a tyrosine kinase of molecular weight 145,000, which is translated only in trace quantities and lacks any in vitro kinase activity. The fusion product expressed by the BCR-ABL gene is hypothesized to lead to malignant transformation because of the abnormally regulated enzymatic activity of the chimeric tyrosine protein kinase. Construction of BCR-ABL fusion genes indicated that BCR