Review article

Overview of chromosomal translocations associated with chronic myeloid leukemia

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ABSTRACT

Chronic Myelogenous Leukemia (CML) is a slow progressing condition caused by balanced translocations of chromosomes 9 and 22, also defined as the Philadelphia (Ph)chromosome, containing the BCR-ABL1 oncogene. CML is classified into three stages; the Chronic, the Accelerated and the Blast crisis phase. These phases are associated with chromosomal translocations and secondary changes. Over the years, innovative scientific development in cancer cytogenetics has considerably improved the detection of chromosomal abnormalities. Fluorescence In situ Hybridization (FISH) method allows further identification of chromosomal alterations that karyotyping cannot resolve. Karyotyping is a gold standard technique that provides the human genome overview. This review mainly focuses on further chromosomal abnormalities, biology of CML, pathways, and therapeutic regimens. The study highlights CML subdivisions and the clinical importance of additional chromosomal abnormalities.

Keywords: CML; Philadelphia chromosome; karyotyping; FISH.

INTRODUCTION

Chronic myeloid leukemia (CML) is a cancer of the hematopoietic progenitor cell that produces balanced translocations of chromosomes 9 and 22, also called as (Ph) chromosome. Translocation of chromosomes 9 and 22 leads to BCR-ABL gene fusion. This oncogene produces proteins (P210 more frequently; P230, P190 more rarely) that generate abnormal tyrosine kinase activity, resulting in abnormal myelopoiesis (1). CML is frequently linked with a procured genetic abnormality; p210BCR/ABL oncoprotein is chiefly found in most of the patients with CML. Two other BCR/ABL proteins, P190 and P230, developed by variant fusion genes, are not often observed in classic CML. Expression of p210BCR/ABL is essential for malignant transformation.

Up to 2000, treatment was confined to generalized agents such as busulfan, hydroxyurea, and interferon-alfa (IFNα). IFNα showed a decrease in the severity of the disease and enhanced the rate of survival but was hampered by its side effects and was fatal. Allogeneic stem cell transplantation (allo-SCT) is therapeutic, however there are risks of causing a disease and is lethal. Moreover, allo-SCT is a choice only for patients with defined organ functions and who has a suitable donor (2). Imatinib mesylate (IM) is an important treatment for CML patients, which inhibits BCR-ABL protein and causes a complete cytogenetic response in majority of these patients, this drug stops the proliferation, activates the mechanism of apoptosis, and generates BCR-ABL expression in cells. Although a small portion of patients with CML are unresponsive to IM (3). Nilotinib (Tasigna) is an alternative drug that forbids tyrosine kinase activity with greater potency and a highly specific for BCR-ABL aside from IM. Tasigna was used as therapy in different phases that exhibited resistance to IM. Nilotinib, well known as IM, adheres to the kinase domain of ABL protein and shows notable function by blocking the signal transduction of BCR-ABL (4).

With a prevalence of 1 to 1.5/100,000 people, CML accounts for around 20% of all forms of leukemia (5). Patients with CML often range from 45 to 55 years (6). CML is extremely rare in children, and its prevalence rises with age. There are unknown hereditary, familial, geographic, ethnic, or economic links to CML, and the disease is neither avoidable nor inherited. The factor responsible for development of the Ph chromosome is unclear in the majority of patients (7).

Etiology

The risk factors in pediatric CML are still unknown. In adults, ionizing radiation is portrayed as a rare predisposing factor. The expansion in CML severity was observed in Hiroshima atomic bomb rescuers after a median of 6 years, CML is caused by the exposure of high doses of radiation and is viewed as a secondary cancer, following irradiation and chemotherapy used in the treating of a cancer mainly Hodgkin and Non-Hodgkin lymphomas (8). Since the incidence of pediatric CML is unelevated in healthy siblings, particularly in twins with one child affected by CML, Genetic factors are important in the pathophysiology of CML. In pediatric CML, function of mutated so-called myeloid ‘driver’ genes is more prominent (9,10).

Staging and classification of CML by phases

CML is usually classified into two stages that is based on the course of the disease and by clinical characteristics: the more indolent (CP) and the more detrimental Advanced Phase, which comprises an initial (AP) and a deadly Blast Crisis Phase (BC). CML has traditionally been classified into three stages based on the number of blasts, leading to the deadly disease. (CML-CP) is the utmost recurrent indolent clinical steady phase of CML that can last for many years. As of now, nearly 90% of CML patients have their conditions identified in the CP. Myeloid cells have differentiated, and there are fewer than 10% blast cells found in bone marrow. The reciprocation to treatment has been outstanding. CML-CP generally heads to the (AP) if left untreated. The cells rapidly proliferate, and the percentage of blast cells maximizes to 10–19%. Besides the Ph+, additional chromosomal aberrations may be identified (11). The retaliation to therapy deteriorates. - CML-AP advances to a (CML-BP) undetectable from acute leukemia, with >20% or 30% of bone marrow blasts of either myeloid or lymphoid immunophenotype. The reaction to therapy is low (12).

Histopathological findings

All patients diagnosed with CML and suspected CML underwent a detailed examination of histologic and immunohistochemical analysis of a bone marrow aspirate. Routine histologic stains are widely used for evaluating the degree of reticulin fibrosis, abnormal megakaryocytes, and neo angiogenesis. According to the literature survey bone marrow fibrosis is a poor prognostication factor in CML (13). It is reported that in responding patients, marrow fibrosis can be regressed by IM. Basophilia is a major predictive factor in CML.

Subtypes of CML

CML includes three subtypes; i) Chronic granulocytic Leukemia (CGL), which is Ph+ and BCR+ with commonly elevated granu1ocyte: nucleated erythroid-cell ratio, majority of megakaryocytes, a increased percentage of small hypo lobulated forms. The mean platelet count is higher than the normal range. The differential leucocyte count shows remarkable peaks in the neutrophils and elevates as the total leucocyte count. ii) Chronic myelomonocytic Leukemia (CMML): is a chronic Leukemia mainly beginning to affect elderly people. Monocytosis is a persistent aspect, commonly linked with neutrophilia, thrombocytopenia, or anemia. Myelodysplastic syndrome is categorized as CMML with low or regular leukocyte counts. CMML with an elevated white blood cell count is myelodysplastic as well as myeloproliferative. iii) Typical CML (aCML): Intermediate between CGL and CMML. Both immature granulocytes and mature neutrophils are dysplastic (14).

Pathways associated with CML

BCR-ABL oncogene pathway in CML

The Ph chromosome causes CML by producing the BCR-ABL1, an activated kinase fusion oncoprotein. Hematopoietic stem cells express ABL1 during development. The BCR-ABL1 gene produces a functional protein that cannot move into the nucleus and is restored in the cytoplasm. where it is linked with leukemogenesis-related kinases (15). Leukemogenesis may be caused by BCR-ABL1 interactions with various pathways. In Ph-positive condition, the proteins (JAK), (STAT) 1, 3, 5, 6 are related to leukemogenesis, c-MYC, an oncogene required for neoplastic transformation, is overexpressed.

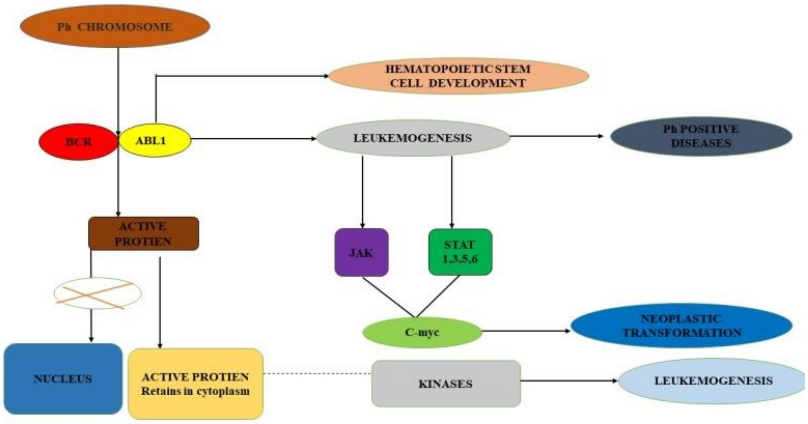

Fig.1: Schematic representation of BCR-ABL pathway Abbreviation: Philadelphia chromosome (Ph), Breakpoint Cluster Region (BCR), Abelson murine Leukemia (ABL), Janus kinase (JAK), Signal Transducers and Activators of Transcription (STAT) 1, 3, 5, 6, Cellular myc (C-myc)

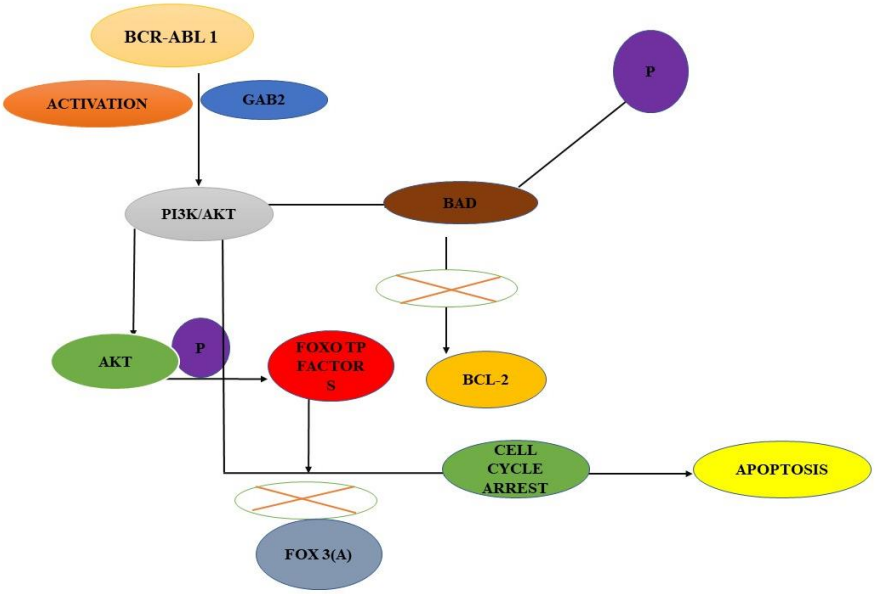

Fig.2: Schematic representation of PI3K–AKT–NF-kB–MM9 pathway Abbreviation: Associated binding Protein (GAB2), Phosphatidylinositol 3-kinase (PI3K/AKT), Forkhead transcription factor (FOXO), B Cell Lymphoma 2(BCL-2), BCL2 associated agonist of cell death (BAD).

PI3K–AKT–NF-kB–MM9 Pathway

BCR-ABL1 stimulates the PI3K/AKT pathway through GAB2. When PI3K/AKT is activated, BAD is phosphorylated, which restricts the antiapoptotic protein BCL-2 from binding to and deactivating it. AKT phosphorylates the FOXO transcription factors, which are also PI3K/AKT downstream targets associated with cell cycle arrest and apoptosis. This inhibits the activity of FOXO3a (16).

Ras–Raf–MEK–ERK pathway

Moreover, the Ras–Raf–MEK–ERK pathway, widely recognized as the Mitogen-activated Protein MAP kinase pathway, is one of the most important signaling pathways in multicellular organisms. After interacting with BCR-ABL1, constitutive Ras activation occurs, resulting in the sequential phosphorylation of multiple Raf–Erk–Mek kinases, which is to recruit several nuclear transcription factors involved in proliferation (17).

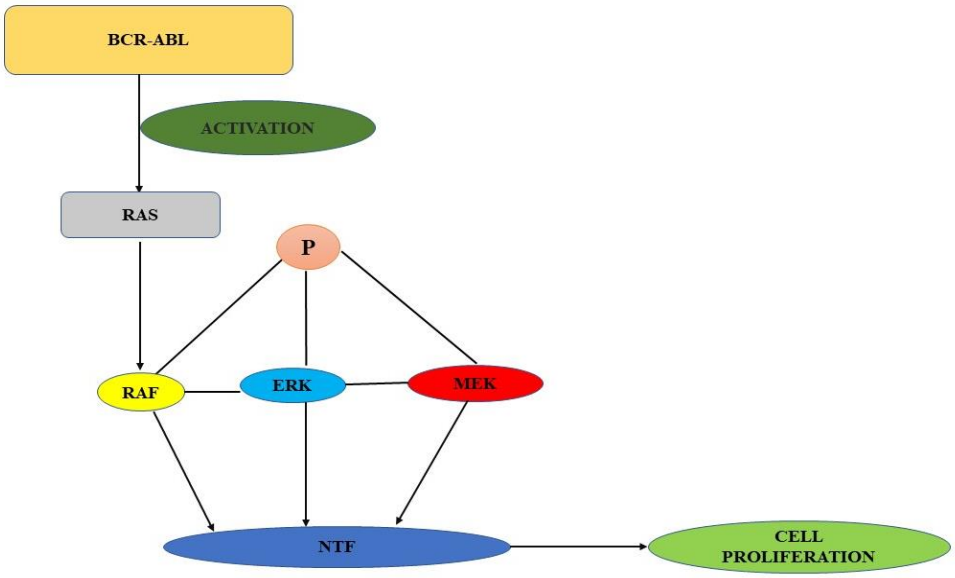

Fig.3: Schematic representation of Ras–Raf–MEK–ERK pathway Abbreviation: Rat Sarcoma Virus (RAS), Phosphorylation (P), Rapidly Accelerated Fibrosarcoma (RAF), Extracellular Signal-Regulated Kinases (ERK), Mitogen-Activated Protein Kinase (MEK), Nuclear Transcription Factor (NTF)

Chromosomal abnormalities

Chromosomal abnormalities, also known as cytogenetic clonal evolution (CE), these entirely nonrandom instances during treatment indicate the progression of the disease and a short life expectancy. These additional chromosomal abnormalities become more common as the disease progresses, rising from 5-10% upon diagnosis in the early stages (CP) to 30% and 80% in the later stages (AP) and (BP), correspondingly. The appearance of additional chromosomal abnormalities (ACAs) and further related genetic disorder is thought to be a keystone of CML's multistep advancement of the disease (18). During cancer, chromosomal translocations are prevalent, some translocations generate oncogenes liable for cancer development. Translocations of chromosomes involves exchange of segments of genetic material between 2 or more chromosomes which is structural chromosomal rearrangements. Trisomy 8, isochromosome 17, and a duplicate Ph chromosome are the most frequently occurring cytogenetic abnormalities seen in CML patients. The current review intends to identify Ph-positive, other complex variant translocations, and (ACA). CML is typically explains the occurrence of the (Ph+), chromosome which is evident in 90 percent of patients. When the (Ph-) chromosome is missing, CML is considered atypical (aCML) and pathobiological differentiated from classic CML. This type of Leukemia is exceptionally rare, with only 1-2 cases per 100 cases of Ph+ CML. Additional chromosomal abnormalities (ACAs) are commonly found in Ph+ cells and are categorized as ‘major’ or ‘minor’ route changes. These modifications impede disease progression and maximize in the late disease stage, from 30% in AP to 80% in BC. They have been linked to a bleak prognosis and a reduced percentage of cytogenetic response to (IM) therapies (19).

Classical abnormalities t (9; 22)

- The (Ph^1) chromosome was the first chromosomal anomaly linked to human cancer. Nowell and Hungerford discovered an abnormally tiny chromosome in the nuclei of CML cells. The BCR/ABL oncogene is thought to cause uncontrolled cell proliferation (20).

- The Ph^1 chromosome, which is formed by translocation of 9 and 22, is observed in 90% of (CML) patients and is responsible for the BCR-ABL fusion of the gene. However, a small percentage of CML patients have translocations with breakpoints other than 9q34 and 22q11 that may be classic or non-classic. Valencia *et al.*, outlines five cases of CML with Ph translocations that included classic translocation as well as reciprocal multiple translocations which were done by G-banding. In all cases, FISH revealed fusion signals on der (22) in all cases (21).

t (Ph) [ins (22;9) (q11; q21q34)

CML has also been associated with several cytogenetic anomalies, patients displaying complex translocation involving a chromosome other than the (Ph). A Ph positive patient with an inserted karyotype expressed in the initial stage had unusual characteristics was described by Wang *et al.*, Insertions are not frequently reported in CML, but if present, they may be a good prognostic factor (22).

- Ikuta *et al.*, described a CML patient with a new complex (Ph) translocation comprising five chromosomes. Chromosomal translocation was difficult to interpret in G banding technique, but spectral karyotyping confirmed a five-way translocation. The (Ph) was formed when a portion of chromosome 9's long arm was linked to the long arm of 22.The SKY method observed a five-way translocation with the karyotype t(4;12;7;9;22). As a result, details of translocation could be determined using SKY, used in cases of complex chromosomal rearrangements (23).

- Al-Achkar *et al.*, discovered an unusual type with the e13a3 BCR-ABL transcript and new complex variant translocation t (9;12;19;22). Other than trisomy of chromosome 8 and an additional derivative chromosome 12, two extra chromosomal abnormalities were seen; however, this translocation in CML has yet to be determined (24).

- According to literature review, the key breakpoints on chromosome 4 are 4p16 and 4q25. Tori *et al.*, reported the first instance of complicated three-way Ph chromosomal variation t(4;9;22) (q21;q34;q11.2).TKI a second generation drug was successfully used as therapy for the patient. The breakpoint at 4q21 is unique (25).

- Yokota *et al.*, described a patient with t (7;11;9;22;9), a complicated five-way translocation. In this translocation, chromosomal breaks occurred on both alleles of band 9q34, but only one of them was involved in the production of BCR-ABL fusion. Sequential rearrangements involving five chromosomes were discovered using the FISH method. The positive response to imatinib treatment recommended that the chromosomal changes were caused by a single event rearrangement (26).

- According to Vaidya *et al.*, chromosomes 9, 11, 13, 19, and 22 have been associated with the complex translocation, as well as (Ph). In this case, the positive reaction to (IM) recommended that the presence of the (Ph) chromosome was the main causative factor. The patient's karyotype was 46, XY, t (9;11;13;19;22) when GTG banding, FISH,

and SKY were used together. On der (11), two distinct translocations were observed: a translocation of 19q and an ABL translocation of 11q. Five-way translocation is an extremely rare event in CML. Only nine cases of 5-way translocation in CML patients were noted in the literature (27).

Non-classical variations

- The chromosomal aberration t (3;12) (q26; p13) is a frequent chromosomal abnormality seen in myelogenous leukemia and is commonly linked with megakaryocyte dysplasia, multilineage involvement, a short duration, any (BP) has a limited duration, and the prognosis is exceedingly bad. Bennour et al. discovered that a patient with Ph positive CML at the (AP) of the disease developed a unique extra aberration t (3;12) (q21; p13) in addition to trisomy 8. As a result, this new chromosomal abnormality involving a 3q21 breakpoint has yet to be characterized. This anomaly is essential in the progression of CML (28).

- Karyotyping analysis of bone marrow found 38-45, XY, t (11;22) (q23; q11.2) (5)/46,XY, t (11;22) (q23; q11.2), but chromosome 9 was not involved. According to Khadir *et al.,* CML variant t (11;22) (q23; q11.2) and BCR/ABL positive is reported first in Turkey (1).

- Leandro *et al.,* discovered an uncommon CML condition with a cryptic (Ph) and a t (1;11) (q21; q23). Hematological cancers, notably acute leukemia, frequently include 11q23 genetic abnormalities. In 85 percent of instances, these mutations disrupt the MLL gene and are linked to a bad outcome. Because 11q23 mutations and MLL are rather uncommon in CML. To evaluate cryptic (Ph) as the product of a variant translocation involving chromosomes 1, 9, 11, and 22, a whole chromosome painting (WCP) of 1 and 11 was analyzed. The data suggested that the cryptic (Ph) and the t (1;11) (q21;q23) had separate origins(29).

- Calderon *et al.,* mentioned a patient having CML who had lymphoblastic blast crisis and monosomy 7 in 71 percent of bone marrow cells; at diagnosis, the karyotype was 45, XX, -7, t (9;22) (q34;q11.2) (20). Moreover, the T315I BCR-ABL mutation was noted. This is the first report of a sequential lymphoid and myeloid blast crisis with distinguished cytogenetic abnormalities (30).

- Ryo *et al.,* study revealed a relatively uncommon chromosomal abnormality in the blast crisis phase that was recognized using G banding and spectral karyotyping. A patient with CML expressed an additional chromosomal abnormality with der (16)t(1;16) (q12; q11.2), which hasn't been seen in CML. Previous research has found increased genetic instability and incomplete DNA repair caused by BCR/ABL1 play a significant role in forming chromosomal abnormalities in CML cells. CML cases with additional chromosomal abnormalities related to 1q or 16q and abnormal chromosomes and further studies in gene mutations are needed to be carried out (31).

- A study including hematologic malignancies and a t (9;22) translocation was published by Gong *et al.,* In addition, five patients (0.36 per cent) had uncommon genetic disorders that recurred (9;22). Two of the five patients had the t (9;11) (p22; q23) abnormality in addition to the t(9;22) (q34;q11) abnormality. In CML 11q23 rearrangements are infrequent, it is estimated that less than 1% of cases are documented. CML with the t (9;22) translocation barely develops the additional t (9;11) translocation during development of the disease. Additional chromosomal changes seen in CML are among the significant markers of progression of the disease (32).

CONCLUSION

Chromosomal translocations play a vital role in the pathobiology of CML. Various chromosomal aberrations, in addition to the Ph chromosome, have been linked to CML. Chromosomal translocations are helpful for applications in clinical diagnostics and will be effective in designing a therapy in the future. Association of techniques such as karyotyping and FISH help unravel genetic alterations in CML patients and detect novel translocations, which can potentially be associated to various phases of the disease and enhance CML diagnostic and prognostic findings concerning CML resistance mechanisms and innovative treatment approaches. Karyotyping and FISH are gold standard techniques in cytogenetics, which could benefit CML patients in CML diagnosis, treatment, and prognosis. Therefore, these techniques help to elucidate uncertainty in additional chromosomal abnormalities in CML and have significant power to forefront precise diagnosis, prognosis and, in the long term, customized therapy.

CONFLICT OF INTEREST

Authors have no conflict of interest.

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