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Milestone Histories and Paradigmatic Genetic Discoveries of Chronic Myeloid Leukemia (CML)

Zhan He Wu

Abstract

Chronic myeloid leukemia (CML) is classified as a hematological malignant rare disease by National Organization for Rare Disease (NORD, USA) based on the estimated incidence of 1–2 cases/100,000 per year internationally. CML occurs in all ages but commonly seen in the 45–55 years group. Males are slightly more affected than females. CML is one of the oldest known diseases with new faces and one of the fastest developing diseases with many extraordinary discoveries in human history of conquering the disease. CML possesses at least Nine First findings in leukemia and cancer research and even in human medical histories: the First named as leukemia in 1845, the First of a live case of CML patient diagnosed in 1846, the First used of arsenic in CML treatment in 1865, the First defined as a myeloproliferative disorder in 1951, the First finding of Philadelphia chromosome (Ph chromosome) in 1960, the First finding of chromosome 9 and 22 translocations in 1973, the First identified as a clonal hematological malignancy derived from the stage of pluripotent bone hematopoietic stem cells in 1977, the First finding of the chromosomal fusion gene-BCR-ABL as an oncogene in 1984, and the First designed target therapy of use of tyrosine kinase inhibitor (TKI) in 1998. The footprints of the studies on CML established the milestone histories. Remarkable and fascinating genetic discoveries were made of the mysteries of human diseases, the multiway translocation of Ph chromosome, and the latest issues. The association of the combination of chronic myeloid leukemia and chronic lymphocytic leukemia will be reviewed in this chapter with the aim of increasing the understanding of CML further from laboratory bench to clinical bedside.

Keywords: rare hematological malignancy, chronic myeloid leukemia, genetic variations, Philadelphia chromosome, BCR-ABL gene

1. Introduction

Myeloproliferative neoplasm (MPN) is a rare type of hematological malignancy featured by the excessive proliferation of single or multilineages of hematopoietic cells in the bone marrow affecting fewer than six in 100,000 people. MPN mainly includes polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (MF), and chronic myeloid leukemia (CML) classified by World Health Organization (WHO) [1].

Among these types of MPN, CML, with several synonyms of chronic myelogenous leukemia, chronic granulocytic leukemia, is the most common type of myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate.

CML consists of about 20% of all leukemias affecting individuals of all ages including children and infants with chronic, accelerated, and blast crisis phases to acute leukemia resulting in life-threatening situation [2].

CML presents as easy bleeding, splenomegaly, feeling run down or tired, fever, loss of weight without trying, loss of appetite, pain or fullness below the ribs on the left side, pale skin, and excessive sweating during sleep (night sweats) [3].

CML has a very exciting history and extraordinary findings in which it has paved the way toward clinical diagnosis and treatment. It was predicted by John Gordon in 2003 that the fascinating CML could be becoming even more fascinating from now on [4].

2. Milestone histories and remarkable genetic discoveries of CML

The remarkable genetic discoveries have been translating into clinical diagnosis, effective, and specific therapies from the following so many FIRST findings.

2.1 The first named as a leukemia

CML was first named as leukemia in the nineteenth century, when it was described and recognized in 1845 from descriptions of the clinical presentations and symptoms by Bennett, Virchow, and Craigie [5–7].

Cells from blood or bone marrow morphology from patient with CML show at every stage differential cells due to partial blockage, unlike the maturation and differentiation of acute leukemia, which are blocked completely in the early cell differential stage. The chronic term of CML refers to maturation and differentiation, unlike other diseases by period of disease duration.

2.2 The first of a live case of CML patient diagnosed

The first live patient with CML was diagnosed in 1846 by Dr. Henry Fuller, a physician at St George's Hospital in London with the identification of a large proportion of abnormal, granular colorless globules under microscope [8].

2.3 The first used of arsenic in CML treatment

Fowler's solution, the compounded a potassium bicarbonate-based solution of arsenic trioxide (As_2O_3) invented by Thomas Fowler named as Fowler's solution in 1786, was first tried in CML among all leukemias in 1865 to reduce the over proliferative white cell numbers [9].

Very excitingly, the arsenic has been used to cure acute promyelocytic leukemia (APL) which it made the worst and incurable type of leukemia; APL became the best therapeutical curable type among all types of leukemias achieved by several Chinese medical researchers [10].

2.4 The first defined as a myeloproliferative disorder

CML was first introduced as a myeloproliferative disorder based on the evidence accumulated of multiple abnormalities involved in erythroblasts, granulocytes, megakaryocytes, but no fibroblasts in bone marrow by Dameshe [11].

2.5 The first finding of Ph chromosome in leukemia

Ph chromosome was first reported in 1960 by Nowell and Hungerford [12]. Originally such a finding was described as deletion of the long arm of chromosome 22, although it was thought to be chromosome 21 [13] and was even thought to be the chromosome Y due to limitation of low chromosomal resolution from the cytogenetic technique at that time [14, 15]. The smart conclusion made from this was the suggestion that such chromosome change could be associated with CML.

Since then the detection of Ph chromosome by the application of the cytogenetic (Karyotyping) and the molecular cytogenetic techniques, fluorescence in-situ hybridization (FISH) has become a very useful and practical approach in the diagnosis and monitor of CML. Cytogenetic karyotype analysis is a specific, accurate, low cost, fast technology in CML diagnosis, and disease monitoring in the detection of both classical and variant Ph translocation.

2.6 The first identified as a translocation of chromosomes 9 and 22 in leukemia

In 1973, Ph chromosome or Ph translocation was identified as balanced translocated chromosomes 9 and 22, t[q34;q11], by Rowley [16]. Such milestone finding identified and classified the Ph chromosome was not the shortening of chromosome 22 as found by Nowell and Hungerford, which it pointed out the direction and narrowed down to the discovery of CML causing gene from the initial finding of the association between Ph chromosome and CML.

2.7 The first finding of BCR-ABL gene in leukemia

Breakpoint cluster region-Abelson leukemia (BCR-ABL) virus was the first finding from CML in leukemia and oncology. BCR-ABL is a fusion oncogene, resulting in CML from the translocation at the breakpoints of the long arm of chromosome 9 and the long arm of chromosome 22 and in humans [17] and mice [18–20].

Studies found that BCR-ABL fusion gene has several types of isoform protein products from the different breakpoints of translocated. The common types are the fusion protein products (p210, p190, and p230), resulting in the enhancement of tyrosine kinase activity in CML and other types of hematological malignancies in the similar mechanism [21]. The concept from such findings obtained provided the valuable theory for the development of the target-specific therapy afterward.

The detection of BCR-ABL gene using PCR technique commonly has become a valuable/effective and sensitive approach in the diagnosis and disease monitoring of CML, which it does not require cell culture.

2.8 The first clinical therapy by using tyrosine kinase inhibitor (TKI) in leukemia

CML has a long developmental history in the trial of treatment in the past, including the first trial by using arsenic (Fowler's solution), x-irradiation, nitrogen mustard, busulfan, hydroxyurea, interferon- α , and stem cell transplantation. The tyrosine kinase inhibitor (TKI) is considered as the first and a successfully designed first-generation target therapy in cancer therapies clinically. This therapy was designed on the base of blocking and deregulating the activity of BCR-ABL fusing gene 1998 [22]. The second-generation TKI started to be used for reducing the resistance was developed in 2004. Such specific therapy significantly prolonged lifespan for patients with CML.

2.9 The first described as a clonal hematological disease in leukemia

Cells from bone marrow or peripheral blood of a patient with CML show excessive proliferation from one or multiple lineages and different maturation stages due to the partial blocking of differentiation.

CML was first identified as a clonal hematological malignancy from pluripotent bone marrow stem cells [23, 24]. Such finding increased our understanding of the stages of disease mechanism and helps in the diagnosis, differential diagnosis, and treatment.

3. Variant complex and multiway translocations of Ph chromosome

3.1 Variant complex translocation of Ph chromosome

Cytogenetically, CML is characterized by the Ph chromosome formed by the fusion gene of the reciprocal translocation $t(9;22)(q34;q11)$, resulting in the chimeric gene breakpoint cluster region (BCR)-Abelson leukemia (ABL).

Studies demonstrated that approximately 90–95% CML patients have Ph chromosome from the classical reciprocal translocations. However, about 5–10% CML cases have variant types of the Ph chromosome. The variant Ph chromosome translocations are involving chromosomes other than 9 and 22 or multiple chromosomes involved in CML cases [25]. Some studies also suggested that the classical and variant Ph chromosome translocations in CML patient have showed different sensitivities to treatment [26].

Mysorekar et al. reported five male CML cases with variant Ph chromosome translocations. Two cases were two-way translocations, $t(16;22)$, $t(15;22)$, and three cases were three-way translocations, $t(1;9;22)$, $t(9;9;22)$, $t(9;14;22)$, and all cases studied were with BCR-ABL fusion gene, but responded well to the tyrosine kinase inhibitors, imatinib treatment in their studied cases [27].

3.2 Three-way translocation of Ph chromosome

Three-way translocation involves three chromosomes including the Ph chromosome. Such complex translocation was found not only in adult but also in childhood.

Lee reported a 22-year-old male CML case with a three-way translocation involving in chromosomes 9, 22, and 11 at the breakpoints of $q34;q11.2;q24$ detected by using cytogenetic-G banding and FISH techniques, and this patient responded well to TKI treatment imatinib [28].

Asif groups reported male CML case with a three-way translocation involving chromosomes 9, 11, and 22 at the breakpoints of $q34;p15;q11$ in separate studies [29].

Allen-Proctor group reported a male CML case with a three-way translocation involved in chromosomes 9, 22, and 17 at the breakpoints of $q34;q11.2;q12$ detected by using cytogenetic analysis of G banding and FISH [30].

Most three-way translocations reported were primary abnormalities. Achkar et al. reported a male CML case with a three-way translocation involved in chromosomes 9, 10, and 22 at the breakpoints of $q34;p11.2;q11.2$ and also loss of Y chromosome as a secondary abnormality after the classical Ph translocation of $t(9;22)$ followed by chemotherapy [31].

CML is very low in childhood and infant. Three-way translocation of Ph chromosome in infant is extremely rare. An 10-month-old boy infant with three-way Ph translocations involved in chromosomes 9, 22, and 14 at the breakpoints of $q34;q11.2;q32$ by using GTG banding and FISH techniques and confirmed the presence of BCR-ABL by

RT-PCR was reported as the first case with the accelerated phase and received favorable response with hydroxyl urea and the TKI (dasatinib) [32].

3.3 Four-way translocation of Ph chromosome

Four-way translocation involves four chromosomes including the Ph chromosome. Asif et al. reported a four-way translocation involved in chromosomes 4, 9, 19, and 22. They have reviewed and analyzed 59 cases of CML with four-way translocations reported from the literatures previously. Their analysis showed that 56% of four-way translocation was male, 39% was female, 2% was missing chromosome Y (-Y), and 3% was unidentifiable of sex [33].

Achkar group reported a four-way translocation involving chromosomes 9, 11, 20, and 22 [34]. The same group reported another case with four-way translocations involved in chromosomes 9, 11, 20, and 22. Also, BCR-ABL fusion gene was detected by reverse transcription polymerase chain reaction (RT-PCR). That patient also showed additional chromosome abnormalities involving translocations of chromosomes 7 and 8. Patient showed poor response to imatinib and died for unknown reason [35].

3.4 Five-way translocation of Ph chromosome

Five-way translocation is involved in five chromosomes including the Ph chromosome. A novel five-way translocation involved in chromosomes 7, 11, 9, 22, and 9 detected by G-banding technique and confirmed by spectral karyotyping (SKY); BCR-ABL gene was detected by fluorescence in-situ hybridization (FISH), which was reported by Yokota group in 2012, and patients showed good respond to imatinib treatment and also reviewed another nine cases of five-way translocations compared with their case reported in that article [36].

Another five-way translocations of 29-year-old male CML case involved in chromosomes 9, 11, 13, 19, and 22 by G-banding technique confirmed by SKY, and BCR-ABL gene fusion by Vaidya group reported a five-way translocation involved in chromosomes 9, 11, 13, 19, and 22, and that case responded well to imatinib treatment [37].

The mechanism of variant complex translocation is still unknown. The spatial arrangement is involved in chromosomes because they require the physical interaction of the translocation partners and the association of genomic instability could be associated with multiway translocation.

3.5 The application of next-generation sequencing (NGS) and the detection of other genes associated with CML

Currently, cytogenetics, FISH, and qRT-PCR have been using as the routine techniques in the applications of CML diagnosis. However, each of them has his/her limitation in the application. NGS technique is a powerful technique with high throughput. Lyu group identified a novel BCR-ABL1 fusion gene with breakpoints in the BCR intron 14 and the ABL1 intron 2 (with an e14a3) by using NGS [38].

Shokeen group studied CML cases by using NGS and found some variants and potential prognostic and susceptibility markers, which helped them in the prediction of TKI therapy [39].

Fu group studied BCR-ABL fusion gene variants on CML by using next-generation sequencing (NGS), and they found an e13a2-like novel form of BCR-ABL fusion, while it was negative with qRT-PCR-based test, which helped them in diagnosis and therapy. Their results suggested that NGS is a powerful technique

to detect BCR-ABL fusion variants, which they could be missed by other routine techniques. In addition, other mutated genes SETBP1, PAX5, and TP53 were also detected [40]. Such findings of additional mutated genes involved in CML by NGS may increase the understanding in leukemogenesis and help in treatment for cases with CML with TKI therapy resistant.

4. Issues of the presence of Ph chromosome or BCR-ABL gene in non-CML hematological malignancies or healthy individuals

Ph chromosome, t(9;22)(q34.1;q11.2), was found in CML at 90–95% as mentioned above [41]. However, Ph chromosome has been found in other types of non-CML hematological malignancies.

Studies showed that acute myeloid leukemia (AML) about 3% of adult AML and 1% in childhood have Ph chromosome [42, 43]. Different proportions of Ph chromosome were found in patient with myelodysplasia syndrome (MDS) [44]. About 20% of adult ALL and 2–5% of children have Ph chromosome in acute lymphoblastic leukemia (ALL) [45–48]. The couple of T-ALL cases with positive Ph have been reported [49, 50]. The presence of Ph chromosome on a patient with lymphoma was detected by a study [51]. Positive Ph chromosome was reported from H929 multiple myeloma cell line [52]. Koshy group reported the presence of Ph chromosome from a case of pregnant women with unusual primary myelofibrosis [53].

Interestingly and surprisingly, BCR-ABL fusion gene was detected in healthy individuals (2/30) but without following up studies seen afterward [54]. Biernaux group studied the BCR-ABL gene of blood cells from healthy individuals and found the presence of BCR-ABL transcript (22 of 73) [55]. More evidence from a study of peripheral blood leukocytes conducted on 16 healthy individuals, and some cell lines as controls by Bose group and results showed the presence of BCR-ABL gene either p210 (27%) or p190 (69%) transcript in healthy individuals [56]. It is suggested that leukemia-associated genes in healthy individuals require the additional activations to be malignancy, although no satisfactory explanation on why BCR/ABL fusion gene detected from some healthy individuals short- and long-term following up.

5. Issues of the combination of CML and chronic lymphocytic leukemia (CLL) in the clonal association

CML and CLL are different hematological malignancies characterized by their cause of disease, their origin of hematopoietic lineages, laboratory findings and clinical presentations, and different immune phenotypes. CML and CLL require different treatment strategies. In general, there are no many problems or issues in the diagnosis and differential diagnosis on both of CML and CLL.

Recently, there were some rare cases reported in the combination of CML and CLL, which raises a question as to whether the myeloid and lymphoid malignant clones derived from the common malignant stem cells or CML and CLL are two independent simultaneous events.

A group performed a study on three-way translocations by flow cytometric sorting using monoclonal antibody anti-CD19 lacked the BCR-ABL rearrangement. Their results suggested CML and CLL were from two different clones B-cell transformation occurred in a Ph-B-cell subset [57].

Wu et al. reported a novel CML case with three-way translocations involved in chromosomes 9, 22, and 11 cytogenetically and confirmed by fluorescence in-situ

hybridization (FISH). It was found the deletion of chromosome short arm (4p) confirmed by comparative genome hybridization microarray. This patient had more than 10 years indolent chronic lymphoblastic leukemia (CLL) history without progression over several years, and cytogenetic test was normal. Interestingly, both CML and CLL got remission after treatment for CML indicating the possibility of the relevant if clonal revolution [58]. These results might indicate the association of Ph chromosome in the leukemogenesis of CML and CLL.

Armarego et al. reported five CML cases in the combination of CLL history and one case with the deletion of short arm of chromosome 17(17p). All patients were treated for both CLL and CML, and a satisfactory outcome was achieved from the five cases studied separately [59].

The association of CML and CLL raises the issues that the combination of CML and CLL is the two different events or a result from a clonal evolution either from CML or CLL that needs to be classified further.

6. Conclusion

CML is a special disease with a milestone history and remarkable nonstopping genetic discoveries, which have paved the path in effective treatment of CML by translating findings into clinical settings.

It is believed that the continuing study on genetic variations will help to develop TKI therapy to minimize further therapy resistance in the future.

CML is an old disease with new face. The continuous discoveries of genetic variations and multiway translocation of Ph chromosome in CML will help in the diagnosis and monitoring of treatment.

The mystery and the associations of the combination of CML and CLL in some reported cases are still unknown.

Such fascinating stories made the best example in the process of conquering the human diseases.


Author details

Zhan He Wu

Western Sydney Genome Diagnostics, The Children's Hospital at Westmead,
Affiliated to University of Sydney, Sydney, Australia

*Address all correspondence to: zhan.wu@health.nsw.gov.au

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