

Mini-Review Article

The Role of BCR-ABL P190 in Diagnosis and Prognosis of ALL patients

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Abstract

Acute lymphoblastic leukemia(ALL) is due to early stage arrest of lymphoblast development. The translocation of Philadelphia (Ph) chromosome occurs as a result of the BCR-ABL fusion gene, which constitutively produced activated tyrosine kinase. This gene fusion is an important indicator for prognosis in ALL and is associated with poor overall survival and remission duration. BCR-ABL could interfere in establishment of ALL. Therefore, in this study, we will try to investigate most pathological aspects involved in BCR-ABL fusion. Strategies for genetic alterations in B-ALL pathogenesis are discussed. Then, the main cytogenetic changes and genetic subtypes for ALL are highlighted. Moreover, intermediate reactions between cancer stem cells (CSC) related to ALL, its niche and microenvironment is discussed. The main objective in this review is to understand the principle prognosis in ALL to introduce new approaches and treatment alternatives.

Keywords: Acute lymphoblastic leukemia, Philadelphia chromosome, tyrosine kinase.

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Introduction

In 1960, Nowell and Hungerford found a small abnormal chromosome belonging to G group known as Philadelphia chromosome (Ph) in seven patients with CML. In 1973, combined banding techniques using quinacrine fluorescence and Giemsa staining showed translocation between chromosomes 9 and 22 t(9;22) (q34;q11) in Ph(1). In early 1980s, a number of genes were mapped, including ABL 1 (v-abl Abelson murine leukemia viral oncogene homolog 1) on chromosome 9, which was mapped using somatic cell hybrids(2). Dekein et al

demonstrated that ABL1 gene on chromosome 9 was translocated to chromosome 9 and lead to development of Ph chromosome. Translocation of ABL1 gene resulted in an abnormal protein with tyrosine kinase activity via formation of a chimeric gene (3). BCR-ABL1 fusion protein shows increased tyrosine kinase activity compared to ABL1 145 KD (4). The chromosomal rearrangement in ABL1 gene and its related fusion ; BCR-ABL1 is predominantly associated with CML and B-acute lymphoblastic leukemia (B-ALL). Currently, other six genes including 1 (4) ETV6-ABL 1 (5), ZM1Z1-ABL 1 (6, 7), EML 1-ABL 1 (8), NUP 214-ABL 1 (9), RCSD 1-

ABL 1 (10-12) and SFPQ-ABL 1 (13, 14) that are able to fuse with ABL1 have been recognized. ABL1 kinase region is conserved and located in N-terminal region of all chimeric proteins, and includes coiled-coil or helix-loop-helix regions (15). Screening for chimeric ABL1 genes could be considered in ALL patients, especially in those with T-ALL, since ABL1 regulates the evolution of T lymphocytes, and plays a pivotal role in the process of their cytoskeleton deformation (16). Although BCR fusion gene has been diagnosed more than 25 years ago, a number of new partner genes for ABL1 have been recently described (17-20). Using cryptogenic assay, this translocation is diagnosed in more than 95% of patients, while using FISH, the remaining 5% of fusion genes located on chromosome 9 or 22 are apparently normal. Moreover, translocation occurs in 25% and 5% of adults and children with ALL, respectively (21). Approximately 75% of ALL children undergo a chromosomal relapse change, which is detected by karyotype, FISH, and molecular techniques. There is common occurrence of genetic changes with reduced favorable outcomes and modification of adverse results such as BCR-ABL1 along with increase in age (22). Cytogenetic tests, FISH and PCR are simultaneously used in combination with diagnosis and monitoring of patients. In diagnosis, the subtype of fusion that depends on BCR breakpoint is important to follow the fusion in patient samples (23). Furthermore, FISH and SNP array have detected CRFL2 (cytokine receptor gene) rearrangement in 7% of ALL children, 5% of whom are associated with Down syndrome (DS-ALL) (23-25). With the exception of tyrosine kinase inhibitors (TKIs) such as imatinib, current therapies are not specific for genetic alterations, and limit the progress of leukemia via short- and/or long-term toxicity. Measurement of low or minimal residual disease (MRD) using molecular techniques is the gold-standard method that detects response to therapy with high sensitivity compared to other routine techniques (26, 27).

Introduction to ALL

B-lymphoblastic leukemia is due to early stage arrest of B-cell development (Figure1). Age and karyotype abnormalities are substantially correlated

with prognosis, and can be used to classify patients to standard- and high-risk (28, 29). Ph⁺-ALL is an aggressive (high-risk) form of acute leukemia that mainly inflicts older adults. In all Ph⁺-ALL leukemic cells, there is reciprocal translocation known as t(9;22), which results in a fusion gene (BCR-ABL) in breakpoint e1a2, generating a 190KD protein with tyrosine kinase activity. This translocation changes several signaling pathways and augment the growth and proliferation of tumor (30). In adults with ALL, Ph chromosome is the most common cytogenetic abnormality with 20-30% incidence in ALL, and 50% of patients have more than 50 years (31). Several studies demonstrated the importance of such adverse karyotypes before development of tyrosine kinase inhibitors (TKIs), when long-term disease free survival (DFS) was rarely higher than 2% without bone marrow transplantation (32-34). Different breakpoints in BCR on chromosome 22 would lead to different proteins with various sizes, including 190 KD (P190) protein especially observed in Ph⁺-ALL, 210 KD (P210) protein with occurrence of 20-40% in Ph⁺-ALL and almost all cases of chronic myeloid leukemia (CML) (35). Heterogeneity of karyotype is also detected in Ph⁺-ALL, including monosomy 7, a high number of Ph chromosomes, t(9;22) (+der(22)), trisomy 8. Deletion of 9P is the most frequent abnormality (36, 37) in this regard. Several studies have shown that the three above-mentioned anomalies are associated with a poor prognosis. Approximately 15% of Ph⁺-ALL patients would have favorable conditions if they are hyperdiploid with 51-67 chromosomes (34, 37).

Indeed, all patients with B-ALL have immune phenotype anomalies which routinely detected by flow cytometric analysis. These immunophenotypes are often related to specific chromosomal abnormalities and can affect prognosis (38, 39). Ph⁺-ALL is substantially associated with a high expression of myeloid antigens, including CD13 (alanine amino-peptidase), CD33 (membrane receptor myeloid lineage), CD66c (Carcinoma embryonic adhesion antigen, related to cell adhesion molecule) and CD25 (receptor α chain of IL-2). Previous studies also demonstrated the importance of gene rearrangement related to phenotypic abnormalities for Ph⁺-ALL compared to Ph⁻-ALL(40-43). For instance, MLL would be related

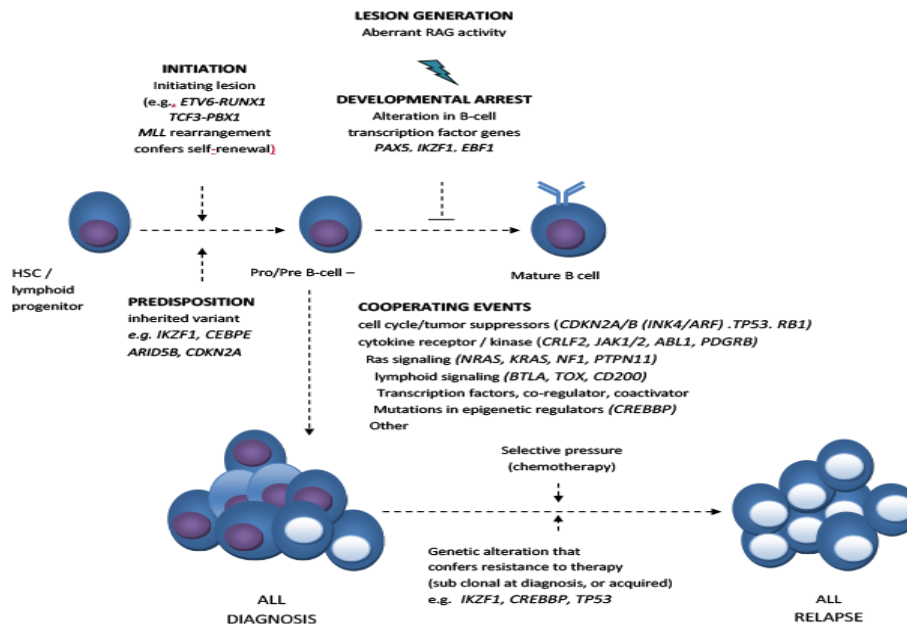


Fig. 1. Proposed model for genetic alterations in B-ALL pathogenesis

to deficiency or/and absence of CD10 (membrane metalloprotease) and CD15 (fucosyl-3- N-acetyl amine) expression (44). Three TEL and AML-1 variants in fusion gene of (TEL-AML1) lead to high expression of CD13 and CD3 and partly CD5. Ig amplifiers of E2A, which binds E2/E47, and homo box of pre-B leukemia (PBX-1) in gene fusion (E2A-PBX1), would rarely express CD13 and CD33 (45). The majority of reports implicate immunophenotypic, karyotypic and molecular subtypes of Ph⁺-ALL before chemotherapy with severe TKIs.

Flow cytometric phenotyping

ALL-wide panel includes CD1 (glycoprotein expressed on membrane of Ag presenting cells), CD4 (membrane glycoprotein), CD8 (trans-membrane glycoprotein), cytoplasmic CD22 (trans-membrane protein), CD79a (Ig α), cytoplasmic IgM, membrane λ and K, CD25, CD58 (lymphocyte function-associated antigen 3), CD66c and CD81 (26 kDa cell surface protein, target of the anti-proliferative antibody-1 (TAPA-1)). Moreover, MRD panel consists of CD10+, CD15+, CD13+, CD19+, CD20+, CD22+, CD25+, CD33+, CD38+, CD38+, CD58+ and CD81+. Expression of CD10, CD20, CD34, and cytoplasmic IgM on lymphocytes is defined as negative (less expression of 20 %), moderate (expression of 20-75%) or positive (75%)

(46).

Genetic and molecular makeup of ALL

Alteration of lymphoid transcription factor of IKZF1 (also known as IKAROS) is a therapeutic strategy for ALL therapy (47, 48). Tyrosine kinase signaling in B-ALL, including CRLF2 (cytokine receptor-like factor 2), ABL1 rearrangement, JAK2, PDGFRB, and mutation in JAK2/JAK1 is treated using tyrosine kinase inhibitors (49-53). Novel mutations in acute T-ALL are mainly including RUNX1 and ETV6 which are tyrosine kinase and epigenetic regulatory, respectively (54, 55). 75% of children ALL types result from a relapse in chromosomal change detected by FISH and molecular techniques (Figure2) (56).

The genetic landscape in ALL

Although ALL would be treated in over 80% of children, relapsed ALL is the main reason of death in them. T-ALL is characterized by mutations of notch1 and rearrangement of transcription factors such as TLX1 (HOX11), TLX3 (HOX11L2), LYL1, TAL1, and MLL. However, all of these chromosomal rearrangements are insufficient to develop leukemia. The majority of involved genes play a role in encoding the proteins related to lymphoid development (PAX5, IKZF1, EBF1, and LMO2), cell cycle regulators of tumor suppression (CDKN2B/CDKN2A, PTEN,

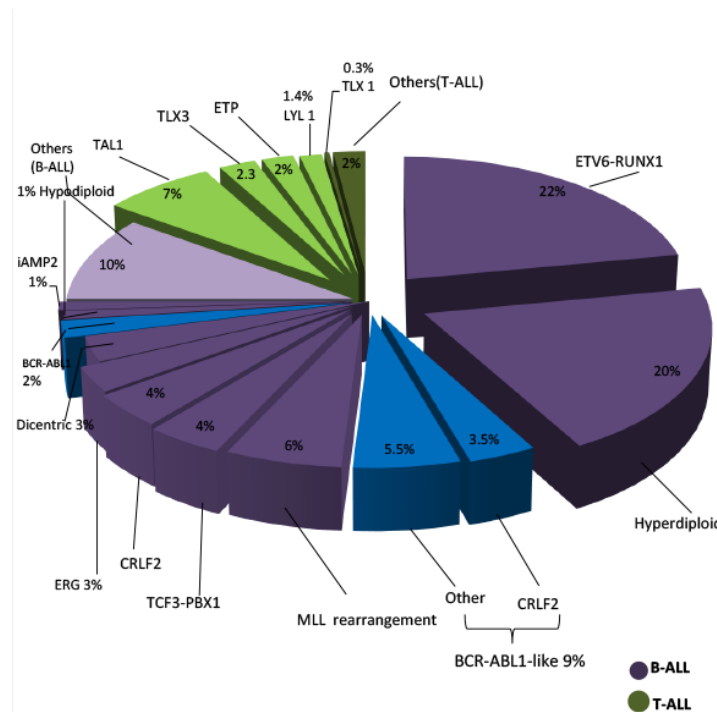


Fig. 2. Occurrence of cytogenetic subtypes in children ALL

RB1), lymphoid signaling (CD200, BTLA, TOX, and glucocorticoid receptor) and transcription mediators as well as combined activities (ERG, ETV6, TBL1XR1). Researchers have managed to show the interaction between CSCs and niche in tumor development (57, 58).

Introduction to molecular function of P230-P210-P190

Groffen et al. identified a breakpoint on chromosome 22 located in 5.8 Kb region known as BCR breakpoint (59). BCR protein has a coiled-coil domain and a tyrosine kinase residue in GRB2-binding site(60). BCR increases dimerization of BCR-ABL and phosphorylates two adjacent oncoproteins on tyrosine in activation loops(61). BCR-ABL protein leads to undesirable proliferation of cells and decreased apoptosis (62-64). ABL1 gene encompasses a region of 230 Kb in 9p34 band containing the first alternative exons 5’ (1a, 1b) and 10 homology exon that count from 2 to 10 (65). The other binding with 1a and 1b exons would express a 6- or 7-kb mRNA with 1143 and 1130 proteins. ABL1 Protein has three SRC homology domains, including SH1, SH2, and SH3. SH1 has tyrosine kinase activity, and is predominant for transformation of oncogenic form. SH2 and SH3 are

involved in protein-protein interactions, and mediate the activation of tyrosine kinase for signal transduction (15). Therefore, these two domains have the main role in regulating and inhibiting the activation of ABL1 (66, 67). Moreover, ABL1 protein has three cores with nuclear signaling, three DNA-binding regions and an F-actin-binding site (68, 69). ABL1 protein plays a role in binding to actin and mobilization, adhesion, receptor endocytosis, autophagy, and facilitating repair after average DNA damage; however, it does not interfere in apoptosis following severe apoptosis (16).

BCR-ABL1 fusion gene

Philadelphia chromosome (Ph) results in t (9;22) (q34;q11), which fuses 5’ region of BCR gene to 3’ region of ABL1 gene and forms a fusion gene known as BCR-ABL1 (Figure 3) (70). Chromosomal breakpoint often occurs between exons 1 and 2 in ABL1 gene (a2). However, a few studies have been reported from breakpoints between exons 2 and 3 (a3). Breakpoints are observed in three separate points of BCR gene, including between exons 13 and 14 (e13a2, previously known as b2a2), exons 14 and 15 (e14a2, previously known as b3a2), implicating major breakpoint region (M-BCR) that transcripts 8.5 kb-mRNA translating p210 (71) (Figure 3, 1B, 1A). Moreover, chromosomal breakpoint can be between

BCR gene exons; 1 and 2 (previously known as e1a2). This breakpoint region is known as minor breakpoint region (m-BCR), which transcribes 7kb-mRNA and p190 (72)(Figure 3, 1c). P210 (major breakpoint in M-BCR) is mainly found in CML, but p190 (minor breakpoint in m-BCR) is expressed in 50% and 80% cases of ph+ ALL in adults and children, respectively (73). Breakpoints occurring in micro breakpoint (μ -BCR) lead to binding between exon 19 of BCR gene and ABL1 gene exon 2 (e19a2 or c3a2), and would produce P230 (Figure 3) (74, 75). The first report on E19a2 transcript was in CNL (chronic neutrophilic leukemia), which accounts for about 1% of classic Ph+ CML cases (75). Other breakpoints and bindings resulting in functional BCR-ABL1 rarely occur, and include e6a2 and e8a2 (76-78). E6a2 transcript has no specific phenotype and has been seen in CML(79), CMML(80), T-ALL

(81), acute basophilic leukemia (82).

BCR-ABL1 like ALL

The majority of 15% of children and/or patients with B-progenitor ALL have well-known chromosomal rearrangement, but often show the expression of genes like BCR-ABL 1+, and have mutation or deletion in IKZF1, which is common in BCR-ABL1 ALL (83). The disease is most common in teenagers and young adults, and has an unfavorable prognosis with survival rate of 62% compared to 85% for cases lacking BCR-ABL1. More than half of the BCR-ABL like cases are due to CRF2 rearrangement and JAK1/2 mutations (84). This disease is successfully treated with TKIs. However, there is a high risk for relapse and treatment failure(53).

Treatment of Philadelphia chromosome in ALL

Historically, chemotherapy alone is associated with a poor prognosis with a median survival of 8

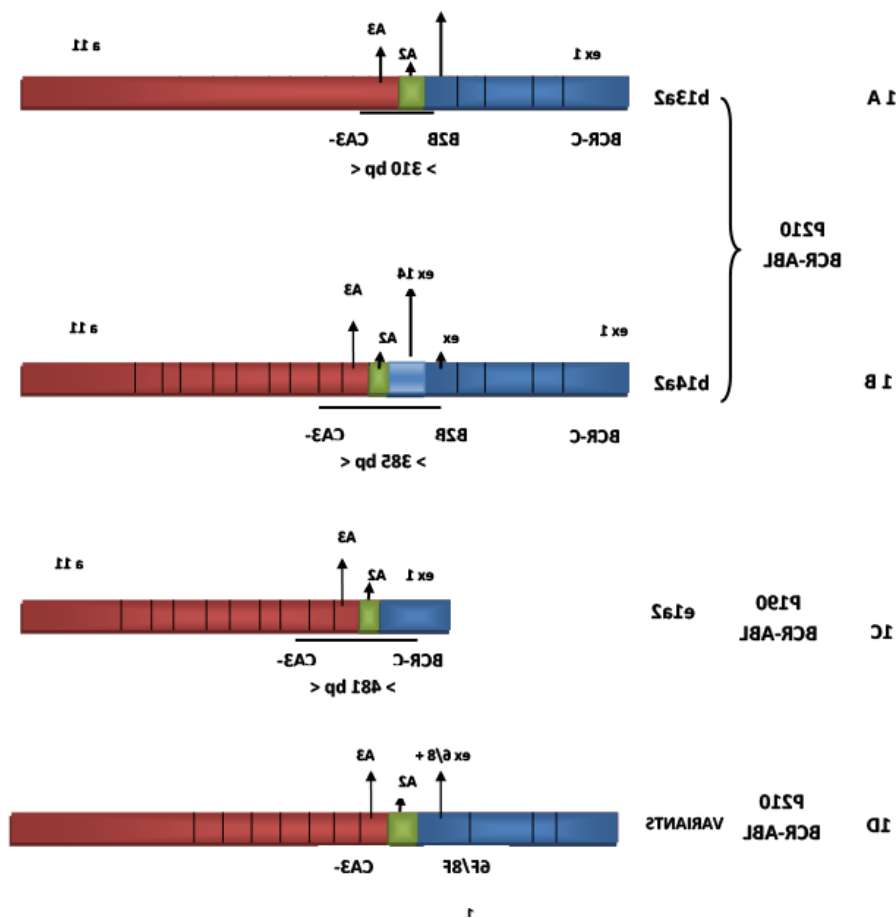


Fig. 3. Schematic view of BCR gene: A-D: Fusion gene depends on specific breakpoint in BCR

months(85, 86). Despite modern treatment with allogeneic hematopoietic stem cell (allo-HSCT) and tyrosine kinase inhibitors (TKIs), resistance to TKIs and its prevalence in elderly patients are still a major problem. Recently, single nucleotide polymorphism (SNP) detects changes in transcription factor gene of IKZF1 (IKAROS)(87-89).

Diagnosis

Early investigation for ALL patients should be included in patient's clinical history and physical analysis with special attention to evidence of CNS or other extranodal involvements. HLA typing of the patient for transplant should be performed at diagnosis. Laboratory evaluation includes assessment of BM aspiration using conventional cytogenetic and FISH with reverse transcriptase polymerase chain reaction (RT-PCR) for P230 and P190 transcriptions to identify BCR-ABL1. The numbers of full transcriptions of BCR-ABL need to be assayed with gene housekeeping measurements. GUS or ABL is analyzed using real-time quantitative PCR (RQ-PCR). In vitro changes may occur, as p190 has not been standardized yet(90).

Remission induction in patients

Yanda et al. reported 86% and 70% complete remission of disease and complete molecular remission in 80 patients with de novo Ph+ ALL, respectively (91).TKIs induces 90% complete remission as front-line of chemotherapy drugs. Imatinib was the first TKIS investigated in Ph+ ALL. Based on ALL center in Germany (GMALL), combination of imatinib and chemotherapy resulted in 95% complete remission and 2-year overall survival of 36% vs 43%, which were statistically non significant (92).

Dasatinib: This was the second YKI produced, which inhibits the family kinases of SRC and ABL, and is 325 times more potent compared to Imatinib. This drug inhibits SRC kinase signaling and mutated ABL kinase and presents a promising long-term efficiency on patients(93-95). In clinical trial II using a combination of dasatinib and hyper-CAVAD conducted by Anderson cancer center (MDACC), 64% have 2-year survival and in 35 previously untreated patients with Ph+ ALL the frequency of event-free survival (EFS) was 57% (96, 97).

Nilotinib: In combination with severe chemotherapy, this drug would induce approximately 90% complete remission, 57% complete molecular remission as well as 71.1%, 49.9% and 62.2% 2-year relapse free survival, RFS, and OS in de novo Ph+ ALL patients, respectively.

Therapy after disease remission and allo-HSCT

Despite a high rate of TKIs-induced remission, this remission is temporary, and reoccurrence would be observed in the majority of patients. The main target of therapy after disease remission is abrogation of minimal residual disease (MRD), which is a main reason for disease relapse. Allo-HSCT substantially increase OS in both pre-TKIs and post-TKIs, and is a proper approach in Ph+ALL patients because of targeting the majority of leukemia cell by intense chemotherapy and graft versus leukemia (GVL) (98).

TKI after transplantation

The unsolved question is how long and in what conditions TKIs required after allo-HSCT for treatment are. In a long-term analysis by the above-mentioned center, 113 Ph+ALL patients were monitored after the first and second CR or active disease. TKI-treatment before allo-HSCT or post-allo HSCT had no significant effect on the outcome of transplantation (99).

BCR-ABL mutations

A prominent and important event in Ph+ALL is therapy resistance for all or advanced TKIs (100). Point mutations in ABL-Kinase domain (ABL-KD) is a common reason for therapy resistance to imatinib, and involves activating loop (A-loop) as well as catalytic domain and ATP binding pocket (P-loop). Moreover, involvement of other signaling pathways is related to SRC family kinase due to mutation of SH2 or SH3 (101).

The role of MRD monitoring

Historically, therapy response is determined by morphologic criteria followed by bone marrow analyses indicating less than 5% blasts in blood. Medical research council (MRC) has showed that complete disease remission for these patients is 45% vs 5% in individual not having the mentioned criteria (102). Patients with complete morphologic remission have mainly leukemic cells known as MRD. Determining MRD is considered as the potential independent prognosis for EFS and OS (103).

Detecting fusion transcription of BCR-ABL by RQ-PCR has a high sensitivity ($\geq 6-10$); however, regulating the proper time and interpretation of results remain uncertain. Furthermore, disagreement of the standard methodology at least for P190 has resulted in different reports. However, consistent effort has been dedicated to create better comparability of PCR results. Therapy course of Pre-TKI indicates a proper correlation between MRD level after induction and/or reinforcement treatment and the outcome of Ph⁺-ALL (104-106). However, opposite results in different time points have been reported to measure MRD (107). Following the introduction of TKIs, the level of BCR-ABL transcription seems to be associated with response (108); however, favorable response has not been determined yet. Lee et al showed that one to three logarithmic change in transcription level of ABL after 4 weeks therapy with Imatinib could prognosticate a high level of DFS and OS (4-year DFS 82.1% vs 41.7%, and 82.3% OS vs 48.6%) (109). Similarly, GRALL AFRO3 has indicated that imatinib improves molecular reoccurrence before transplantation that would cause a better transplantation outcome (110). In contrast, Based on the Yanda et al's study, the rapid molecular remission and its outcome are not associated with imatinib-basic chemotherapy (100, 101). Disease relapse risk originates from pre-existing sub clones with point mutations in BCR-ABL kinase domain (111). However, they have not indicated a significant correlation between positive MRD and reoccurrence in patients treated with imatinib-based chemotherapy. Wassmann et al reported imatinib-induced molecular remission in MRD⁺ patients after allo-HSCT. MRD⁺ patients predict a definite recurrence after 6-10 weeks therapy with imatinib. Therefore, timely intervention is suggested in remission of MRD⁺ patients despite common evidence from MRD monitoring (112).

Conflicts of Interest

The authors declare that they have no conflict of interest in this work.

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