**Review Article**

# Imatinib Resistance and Relapse in CML Patients with Complex Chromosomal Variants

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Abstract

The BCR-ABL tyrosine kinase inhibitor Imatinib is highly effective for chronic myeloid leukemia (CML). However, some patients gradually develop resistance to Imatinib, resulting in therapeutic failure. In the present study, we analyzed 192 CML patients, from which CML relapse was observed in 17 individuals with involvement of other chromosomes in addition to Philadelphia translocation and who were on treatment of Imatinib (400mg per day since last 3-4 years).  Interestingly, all 17 individuals had only BCR/ABL fusion at the time of diagnosis and attained complete Cytogenetic and hematological remission (CHR) within 18 weeks of the therapy.   Three individuals among these 17 were not regular in the uptake of Imatinib after attaining CHR and CCyR and could be probable reason for relapse.   In addition, we have also recorded primary resistance to Imatinib in 4 individuals who were diagnosed with some complex chromosomal variants.   Therefore, either involvement of other genes along with BCR/ABL fusion, or additional chromosomes and point mutation in the fusion BCR/ABL gene itself could be a reason for primary resistance and relapse to Imatinib.

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# Introduction

Chronic Myeloid Leukemia (CML) is attributed to the chromosomal translocation t(9;22)(q34; q11), yielding the Philadelphia (Ph) chromosome. This translocation generates a fusion gene that encodes BCR-ABL, an active protein tyrosine kinase gene. The resulting BCR-ABL (breakpoint cluster region-Abelson) fusion protein is a constitutively active tyrosine kinase, conferring enhanced proliferative activity and decreased sensitivity to apoptotic cell death in the cells in which it is expressed.

Imatinib (Gleevec, formerly STI571; Novartis Pharmaceuticals) is a 2-phenylaminopyramidine compound that is a potent inhibitor of all ABL tyrosine kinases (c-ABL, BCR-ABL, and Tel/ABL). In addition, Imatinib is an inhibitor of the tyrosine kinases of the platelet-derived growth factor (PDGF) receptor [1], , ARG [2], and c-Kit, and the macrophage colony-stimulating receptor, c-fms.

Clinical trials have demonstrated the efficacy of Imatinib in chronic-phase CML[3]. Approximately 95% of patients with *de novo* chronic-phase CML achieve complete hematologic response, while 90% achieve major, and 80% complete, cytogenetic remissions. It is effective as a single agent in the treatment of CML patients, with the most encouraging results seen in patients in chronic phase (CP) disease.

Although Imatinib is widely recognized as the standard of care in the first-line treatment of chronic myeloid leukemia (CML); however, resistance can limit its long-term benefits. Early identification of the loss of response to Imatinib is therefore important for the optimal management of patients with this type of leukemia. Cytogenetic and molecular responses during the first 12 months of treatment have been shown to predict future responses (complete cytogenetic response and major molecular response) and reduce disease progression [4]. The degree of early reduction in BCR-ABL levels after commencing Imatinib therapy is a good indicator of subsequent response. Monitoring for kinase domain mutations should also be considered in patients with suboptimal response or in those who demonstrate resistance. Modification of the treatment strategy is required if there is a loss of response.

Resistance to Imatinib can be categorized according to the time of onset: primary (intrinsic) resistance is a lack of efficacy from the onset of treatment with Imatinib and secondary (acquired) resistance (relapse) is defined as an initial response followed by a loss of efficacy with time of exposure to Imatinib. According to the clinical and laboratory criteria used for detection, resistance could be further subdivided into hematologic, cytogenetic, and molecular resistance.

# Materials and Methods

Conventional cytogenetic analysis was performed on un-stimulated 24-hour culture of a bone marrow (BM)/Peripheral Blood specimen. The cells were cultured and processed by conventional methods, and the chromosomes were stained with Trypsin-Gyms Banding (GTG-banding). The karyotype was described according to the International System for Human Cytogenetic Nomenclature (ISCN, 2009)

FISH was performed on uncultured bone marrow/blood cells by using BCR/ABL dual color dual fusion probes from Kreatech Diagnostics. Fluorescent signals were observed under Axio Scope A-1Microscope (Carl Zeiss, Germany) attached with Progress C-5 Camera. In manual investigation 200 cells were analyzed.

Follow up was performed at every 3 to 6 month and Cytogenetic response to therapy was defined relative to the percentage of Ph+ metaphases identified by chromosome banding   analysis: complete if 0%, partial if from 1% to 34%, minor if from 35% to 95% and none if greater than 95%   Ph+ metaphases were

detected.

# Result and Discussion

In the present study from 192 CML diagnosed individuals, we noticed that 21 individuals (4 at diagnosis, 11- chronic phase and 6-accelerate phase) developed primary or secondary resistance to imatinib (Gleevec) while rest all have achieved CHR and CCyR. Out of 21 individuals, 17 were on imatinib treatment since last 3-4 years with a dose of 400mg/day.  At the time of diagnosis, all these 17 individuals had only BCR/ABL fusion;  t (9; 22)(q34; q11.2) and all had achieved complete hematologic response (CHR), complete cytogenetic response (CCyR) and major molecular response within 12–14 months from their treatments with Imatinib. Real-time quantitative polymerase chain reaction (RT-qPCR) suggested *a BCR−ABL/BCR ratio of* 0.001% which indicates MMR [5,6]. At the molecular level, significant reduction in the level of *BCR-ABL* transcript has been measured by quantitative real-time PCR (RQ-PCR). CML relapse was observed in these 17 individuals along with extra chromosome i.e trisomy14, trisomy 17, trisomy 19, trisomy 21, iso(17q) and marker chromosome beside with BCR/ABL fusion in their follow up study (Fig.1a) (Table 1). The dose of Imatinib increased from 400mg/day to 600mg/day in these 17 individuals, which also failed to achieve CHR and CCyR and MMolR. They have been switched on to second generation tyrosin kinase inhibitor (dasatinib/nilotinib). No further study was available for this individual weather this next generation Tyrosin kinase inhibitor helped to achieve remission or not.
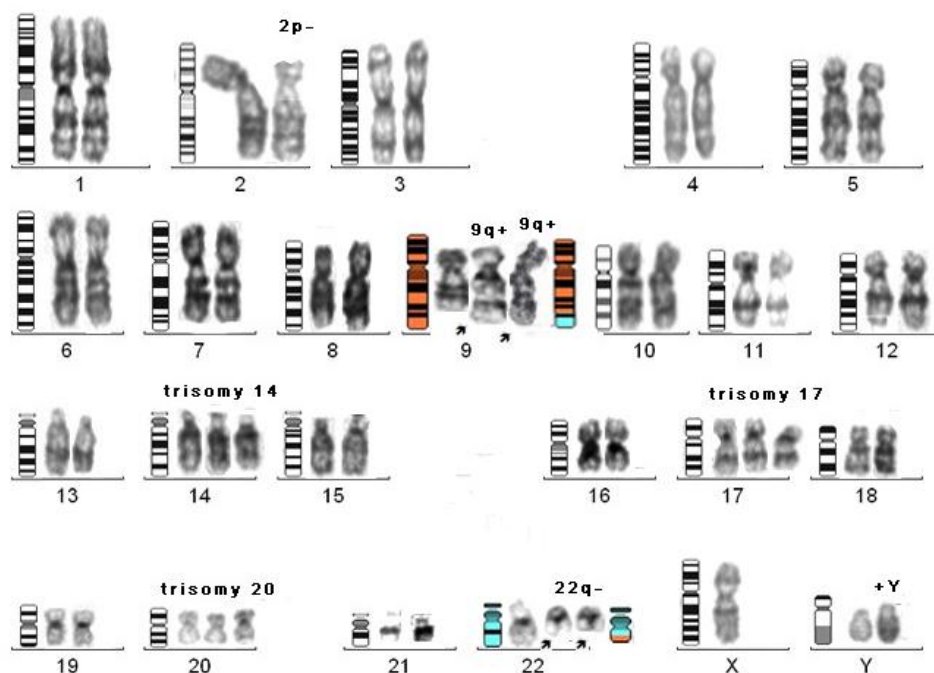


**Figure 1a**    52,XY,+Y,del(2p),+9,add(9q)t(9;22)(q34;q11.2)×2,+14,+17,+20,+22,der(22) t(9;22) (q34;q11.2)×2
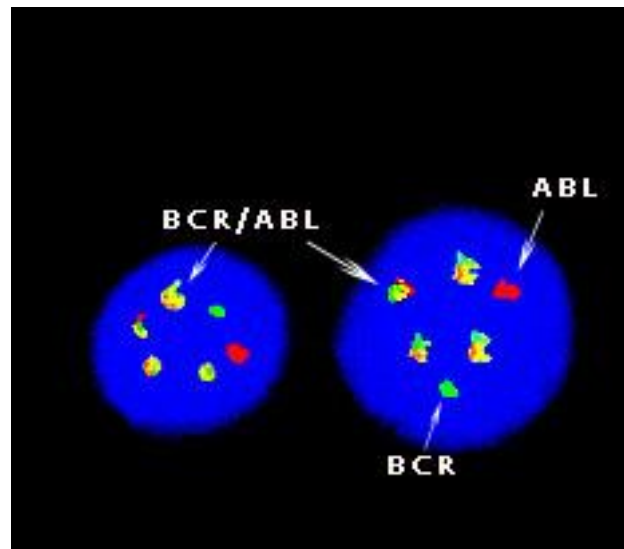
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**Figure 1b** signal pattern: 4F1R1G: which suggest t (9; 22) X2 (additional Philadelphia chromosome)

**Table 1**   Cytogenetic and hematological finding in CML Relapse patients.

| Sr | Age/sex | Years on | Cytogenetic   relapse study | Total   WBC |
|----|---------|----------|------------------------------|-------------|
| 1 | 42/F | 4 | 68,XXX, der(9)add (9q)X2,-17,iso(17)(q11.2) ,+der(22)del(22q)X2 | 22000/mm$^3$ |
| 2 | 39/M | 4 | 47,XY,+8,t(9;22)(q34;q12),iso(17q) | 19000/mm$^3$ |
| 3 | 45/M | 3 | 47,XY,+8,t(9;22)(q34;q12),iso(17q) | 19500/mm$^3$ |
| 4 | 41/M | 3.5 | 48,XY,+8, t(9;22)(q34;q11),iso (17)(q),+21 | 21000/mm$^3$ |
| 5 | 31/M | 3 | 47,XY,+8[15]/46,XY,t(9;22)(q32;q12)[10] | 16000/mm$^3$ |
| 6 | 33/M | 3 | 47,XY,+8[12]/46,XY,t(9;22)(q32;q12)[08] | 19000/mm$^3$ |
| 7 | 48/M | 3.5 | 45,X,-Y, t(9;22)(q34;q11) | 20000/mm$^3$ |
| 8 | 52/M | 3 | 52,XYY,del(2p),+der(9)add(9q)×2,+14,+17,+20,+der(22)del(22q)×2 | 29000/mm$^3$ |
| 9 | 36/F | 2.5 | 45,XX,-7,t(9;22)(q32;q12) | 54000/mm$^3$ |
| 10 | 49/F | 2 | 45,XX,-7,t(9;22)(q32;q12)[16]/45,XX,-7[06]/46,XX,t(9;22) (q34;q12)[4] | 48000/mm$^3$ |
| 11 | 36/F | 2.5 | 45,XX,-10,-13,+mar/46,XX,9q+,+mar/46,XX,t(9;22)(q34;q12)/46,XX | 26000/mm$^3$ |
| 12 | 36/M | 3 | 48,XY,+8,t(9;22)(q34;q12),+19 | 28000/mm$^3$ |
| 13 | 34/F | 3 | 47,XX,+6/46,XX,t(9;22) )(q34;q12)/48,XX,+6,+8,t(9;22) (q34;q12) | 35000/mm$^3$ |
| 14 | 56/F | 3 | 68,XXX, der(9)add (9q)X2,-17,iso(17)(q11.2) , +der(22)del(22q)X2 | 33000/mm$^3$ |
| 15 | 72/M | 3.6 | 46,XY/47,XY,t(9;22)(q34;q11),+mar | 31500/mm$^3$ |
| 16 | 29/M | 3 | 47,XY,t(9;22) )(q34;q12)/46,XY,Iso(17q) | 22000/mm$^3$ |
| 17 | 31/M | 3 | 47,XY,t(9;22) )(q34;q12)/46,XY,Iso(17q) | 19500/mm$^3$ |

Four individuals were having complex three ways translocation along with some secondary abnormality at the time of diagnosis (Fig.2a&3a) (Table 2). They were given Imatinib 400 mg/ day for 6 month but they failed to achieve CHR, CCyR and MMR. Then the dose was increased by 600mg/day for another 5-6 months where partial hematological remission (PHR) was achieved with approximately 85-90% Ph+ cells. Involvement of other chromosome in this complex translocation could be a probable reason for Imatinib resistance or prolong imatinib response [7].
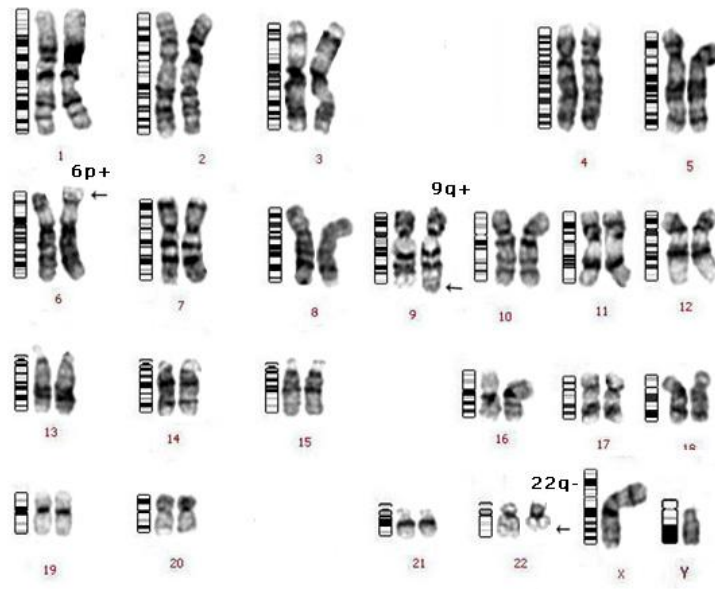


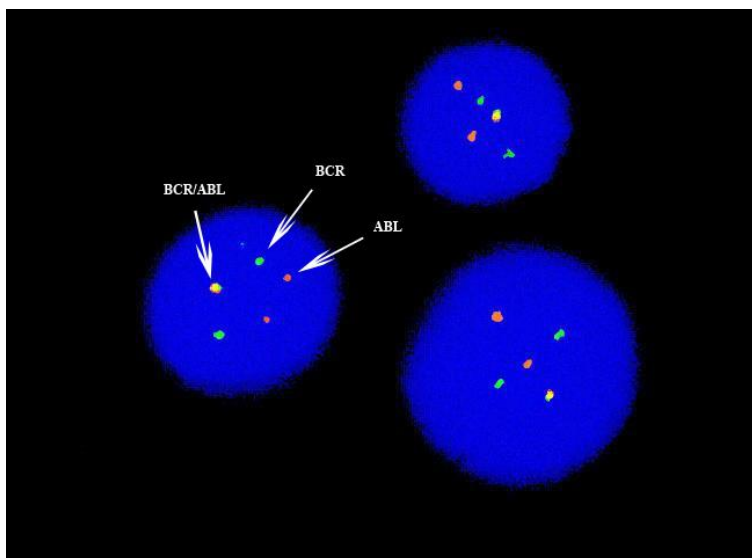**Figure    2a**        46,XY,t(6;9;22) (p22;q34;q12)



**Figure 2b** signal pattern   1F2R2G  : which suggest variant (three or four way translocation)

Table 2    Cytogenetic and hematological findings in patient with primary resistance to imatinib

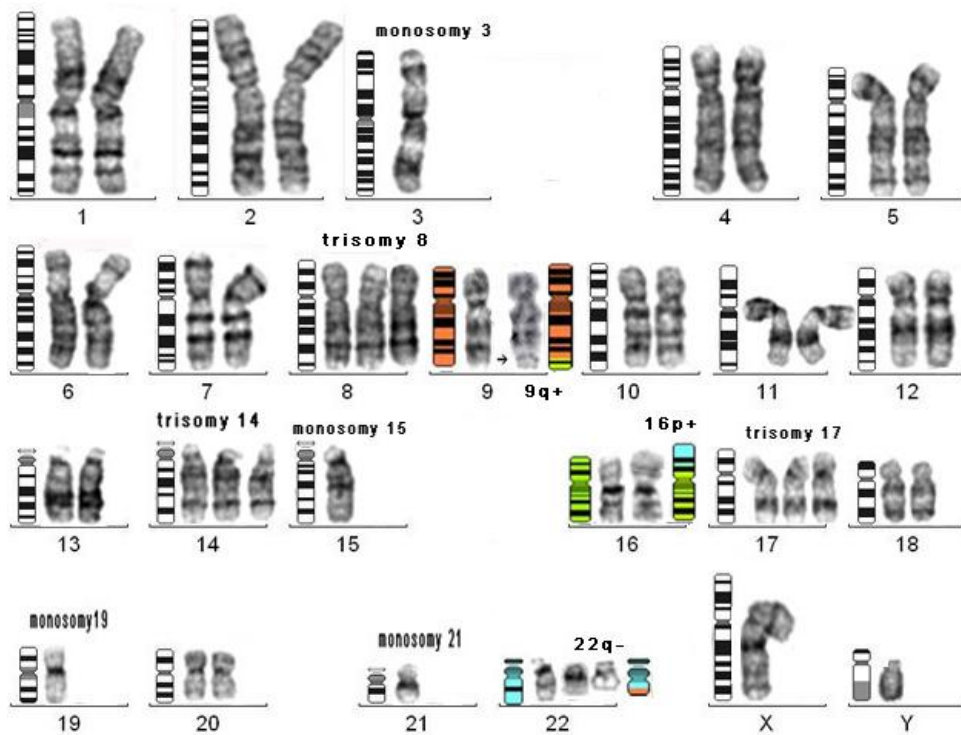| Sr no | Age/sex | Years on Imatinib | Cytogenetic study | Total WBC count |
|-------|---------|-------------------|-------------------|-----------------|
| 1 | 33/M | 1.2 | 46,XY,t(3;9;22)(q26;q34;q12) | 72000/mm$^3$ |
| 2 | 34/F | 1.6 | 46,XX,t(6;9;22) (P22;q34;q12) | 92000/mm$^3$ |
| 3 | 41/M | 1.6 | 46,XY.-3,+8,t(9;22;16)(q34;q11.2;p12),+14,-15,+17,-19,-21,+der(22)del(22q) | 10000/mm$^3$ |
| 4 | 37/F | 1.8 | 45,XX,del(5q)(q22),t(9;22)(q34;q12) | 120000/mm$^3$ |



**Figure   3a**      46,XY,-3,+8,t(9;22;16)(q34;q11.2;p12),+14,-15,+17,-19,-21,+der(22)t(9;22)(q34;q11.2)
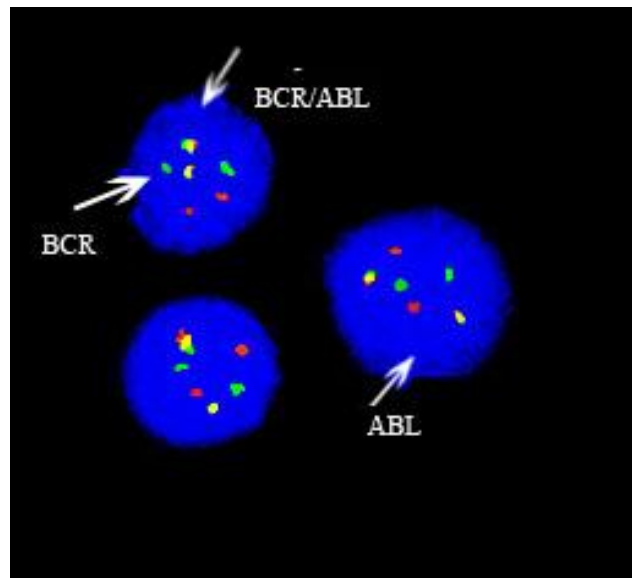
**Figure 3b** signal pattern 2F2R2G

The incident of both typical and atypical BCR/ABL gene rearrangement was observed when we perform FISH (Fluorescence In Situ Hybridization) by using BCR/ABL dual colour dual fusion probe (Kreatech diagnostics, The Netherlands). Majority of individuals shows typical signal pattern of DF-FISH, 2F1R1G, while few shows 4F1R1G signal pattern (Fig.1b) which is an indication of extra Ph+ chromosome. Atypical signal pattern of 1F2R2G (Fig.2b) and 2F2R2G (Fig.3b) was also observed in 3 individual which indicates complex translocation with additional partner along with extra Ph+.

Molecular monitoring of the BCR-ABL transcript in chronic myeloid leukemia (CML) using quantitative RT-PCR provides important diagnostic and prognostic information.Karyotyping, FISH, and real-time PCR give reliable results but differences due to measurement of altered target structures have to be kept in mind when using these data for definition of remission status. Correlations between all methods applied were highly significant. Conventional RT-PCR measure BCR-ABL transcripts on the m-RNA level and are therefore dependent on the transcription rate of BCR-ABL. Despite the fact that chromosome analysis, FISH, and RT-PCR measure BCR-ABL positivity on different biological levels and is dependent on different parameters. In the vast majority of CML patients, and in up to 35% of Philadelphia chromosome-positive precursor B-ALL, the breakpoint on chromosome 22 is located between exons 12 and 16 (b1 to b5) of the BCR gene, in the major breakpoint cluster region (M-bcr). The M-bcr transcription product has two junctional variants, b2a2 and b3a2 that give rise to the BCR/ABL1 chimeric protein p210, a deregulated tyrosine kinase. In a small minority of CML patients and in a majority of patients with Philadelphia chromosome positive precursor B-ALL, there is a minor breakpoint region giving rise to junctional variant e1a2, which codes for the BCR/ABL1 chimeric protein p190 [8].

The breakpoints within the ABL1 take place either upstream of exon Ib, downstream of exon Ia, or, more frequently, between exons Ib and Ia [9]. In most patients with CML and in one-third of those with Ph-positive B-cell acute lymphoblastic leukemia (Ph+ B-ALL) the breakpoints within BCR map to a 5.8-kilobase (kb) area spanning exons e12-e16 (formerly called b1-b5), referred to as the major breakpoint cluster region (M-bcr). Alternative splicing gives rise to fusion transcripts with either b2a2 or b3a2 junctions that generate a 210-kDa protein (p210BCR-ABL1) [10]. There is controversy in the

literature about the use of peripheral blood and bone marrow for the monitoring of BCR/ABL1 level in chronic myeloid leukemia. The differences and correlations of BCR-ABL mRNA between peripheral blood (PB) and bone marrow (BM) assays    depends on the depth of the molecular response in BM for CML during imatinib therapy [11], whereas few    study suggest that peripheral blood is in concordant with bone marrow and can be used to monitor the disease [12]. In the present study we also found no difference in the use of peripheral blood and bone marrow in the monitoring of disease and remission. Variant Philadelphia (Ph) chromosome translocations have been reported in 5%-10% of patients with newly diagnosed chronic myeloid leukemia (CML) [13]. Variant translocations may involve one or more chromosomes in addition to 9 and 22. Presence of variant translocations has no impact on the cytogenetic and molecular response or on outcome, regardless of the involvement of different mechanisms [14-16], however, in the present study, when BCR/ABL1 transcript was performed in patient with complex translocation; we observed Minimum molecular remission (MMR) to imatinib instead of complete molecular remission. A point mutation in the BCR/ABL1 transcript could be a one of the reason for these MMR in patient with complex translocation and analysis of such mutation in BCR/ABL1 transcript will help to monitor effect of imatinib and remission.

Patients can be classified (Table 3) according to their response to treatment, which can be considered optimal, suboptimal, or failure [17, 18]. Failure indicates that primary resistance patients in this category should be switched to another treatment. Patients in the suboptimal category may still benefit from continued treatment with Imatinib, but a favorable long-term outcome is not probable at the current dose. Resistance to Imatinib may be due to other genes involved along with BCR-ABL fusion or point mutation in the BCR-ABL kinase domain. To date, more than 50 different *BCR-ABL* kinase domain mutations have been found to be associated with Imatinib resistance [19, 20]. A point mutation in *BCR-ABL* kinase domain can cause an amino acid change, which impairs the critical contact points of Imatinib binding or alters the conformation of the protein. BCR-ABL1 mutation analysis is recommended to facilitate selection of appropriate therapy for patients with chronic myeloid leukaemia after treatment with imatinib has failed, since some frequently occurring mutations confer clinical resistance to nilotinib and/or dasatinib [ 21].

Table 3 Operational Definition of Failure and Suboptimal Response for Previously Untreated Patients in Early Chronic Phase Chronic Myeloid Leukemia Treated with Imatinib 400 mg/day

| Time After Diagnosis (months) | Failure | Suboptimal Response |
| --- | --- | --- |
| 3 | No HR (stable disease or disease progression) | Less than CHR |
| 6 | Less than CHR, no CyR (Ph+ >95%) | Less than PCyR (Ph+ >35%) |
| 12 | Less than PCyR (Ph+ >35%) | Less than CCyR |
| 18 | Less than CCyR | Less than MMR |
| Anytime | Loss of CHR, loss of CCyR, mutation | ACA in Ph+ cells, loss of MMR, mutation |

ACA=additional chromosome abnormalities; CHR=complete hematologic response; CCyR=cytogenetic response; HR=hematologic response; MMR=major molecular response; PCyR=partial CyR; Ph+=Philadelphia chromosome positive.

Trisomy 8 and iso(17q) are most commonly involved as a secondary abnormality in CML. Controversial studies found in the literature regarding additional chromosomal abnormality and survival or therapeutic response in chronic phase. Various secondary chromosome abnormalities and multiple clones results in shorter survival in CML patients [22]. The prognostic significance of the secondary genetic changes is not uniform, although abnormalities involving chromosome 17, e.g., i(17q), have repeatedly been shown to be ominous additional cytogenetic and molecular genetic aberrations is most likely modified by the treatment modalities used [23].

# Conclusion

Chromosome analysis is still the gold standard for diagnosis and follow-up studies in CML. Especially in good responder's sensitivity of chromosome analysis are too low to detect residual disease. Periodic (every 6–12 months) cytogenetic monitoring for karyotypic abnormalities is critical throughout imatinib therapy to detect clonal evolution even in cases of early CCR. In the present study we found primary resistance to imatinib in 4 CML diagnosed individuals who had complex chromosomal rearrangement, despite low numbers, in our experience patients carrying complex Ph+ translocations do differ significantly in hematological and clinical features from those with standard translocation. while CML relapse were observed in 17 individuals with involvement of other chromosomes along with Ph+, further we observed that 3 patients out of this 17 were irregular in the uptake of Imatinib after achieving CHR and CCyR after 12-14 months of therapy with imatinib, so secondary abnormality and irregularity in uptake of imatinib could be a reason for relapse and resistance to Imatinib. Detection of BCR-ABL mutants prior to and during the course of Imatinib therapy may aid in risk stratification as well as in determining therapeutic strategies.

Imatinib dose escalation may be considered in some patients who experience a loss of response on 400 mg/day Imatinib or in those with low Imatinib plasma levels. Treatment should be changed to Dasatinib or Nilotinib if a response is lost in patients who received higher doses of Imatinib (i.e., 600–800 mg/day) or if Imatinib-resistant mutations emerge however data about the outcome of patients with variant translocations after therapy with next generation tyrosine kinase inhibitors are limited.

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