IJCRR
Vol 05 issue 10
Section: Healthcare
Category: Case Report
Received on: 17/04/13
Revised on: 02/05/13
Accepted on: 19/05/13

CHROMOSOMAL ABNORMALITIES IN PHILADELPHIA CHROMOSOME- NEGATIVE CELLS IN PATIENT WITH CHRONIC MYELOGENOUS LEUKEMIA TREATED WITH FIRST GENERATION TYROSINE KINASE INHIBITOR- SINGLE CENTER EXPERIENCE

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ABSTRACT

Chronic myelogenous leukemia (CML) is characterized by the presence of a Bcr-Abl fusion protein with deregulated tyrosine kinase activity that is required for maintaining the malignant phenotype. Imatinib as a selective inhibitor of Bcr-Abl induces complete cytogenetic remission in the majority of patients with CML in chronic phase. Targeted therapy of CML with imatinib favors the manifestation of Ph-(negative) clone disorders in some patients. Facts indicate that patients on imatinib should be followed with conventional cytogenetics, even after induction of complete remission.

We report a case of a patient with CML, in chronic phase treated with imatinib which induces the most common abnormality trisomy 8.

Keywords: Chronic myelogenous leukemia, imatinib, Philadelphia chromosome, clone evolution

INTRODUCTION

CML is a myeloproliferative disorder characterized by a specific cytogenetic abnormality, the Philadelphia chromosome (Ph), a balanced translocation, involving a fusion of the Abelson oncogene (ABL) from chromosome 9q34 with the breakpoint cluster region (BCR) on chromosome 22q11. The molecular consequence of this translocation is the generation of a BCR-ABL fusion oncogene, which translates into Bcr-Abl oncoprotein with increased tyrosine kinase activity. This increased tyrosine kinase activity of the Bcr-Abl protein is essential to its transforming capability as well as its increased binding to actin cytoskeleton (1).

Current thinking holds that the initial Bcr-Abl translocation occurs in a hematopoetic stem cell that, by the virtue of the Bcr-Abl protein, acquires a proliferate advantage over normal hematopoesis. CML has a biphasic or thriphase clinical course: 90% of the patients are diagnosed in the chronic phase, but the disease eventually evolves to a blastic phase unless successfully treated. Approximately two-thirds of the patients manifest an accelerated phase. A distinct feature of the disease progression is the appearance of additional cytogenetic abnormalities in the Ph+ cells (2).

This phenomenon know as clone evolution, frequently involves a second Ph, trisomy of chromosome 8, abnormalities of chromosome 7. Clone evolution is considered as a criterion of accelerated phase, but when it represents the only criterion of transformation, it is associated with a better prognosis than other criteria of accelerated phase. Standard therapies for CML are inhibitors of tyrosine kinase (TKI) like imatinib mesilate (STI 571, Glivec). Imatinib a small molecule, targets and inhibits the Bcr-Abl tyrosine kinase by competitive binding at the ATP-binding site(3).In patients with newly diagnosed chronic-phase

CML, treatment with imatinib results in a high rate of complete cytogenetic remission(up to 87% in the Iris study)(4).An update of this study after 5 years of follow-up supports the earlier results, with hematological remission rate of 98%, a major cytogenetic response rate of 92%, a rate of complete cytogenetic response rate of 87% and progression free survival in 84% of the patients(4). During the administration IFN-alfa, cytogenetic abnormalities have been reported to occur in Ph-negative cells (5).

Isolated examples of similar phenomenon have been reported in patients treated with imatinib (6).An article of Bumm et al. draws attention to the occurrence of clone karyotypic abnormalities in Ph chromosome (Ph) negative cells following imatinib induced cytogenetic response. To date more than 20 such cases have been described with the most common abnormalities trisomy 8 and chromosome 7 defects. All were late chronic phase and had received prior therapy. Various explanations for this phenomenon have been proposed.

We report a case with CML in chronic phase treated with imatinib with the most common abnormality.

CASE REPORT

A 62-year-old female (N.R) was diagnosed with CML in chronic phase after routine blood count estimation in June 2000. The hematological workup at diagnosis revealed hemoglobin level was 12,1g/dl, white blood cells count of $133,7x10^9$/l without leukemic blasts, eosinophils and basophils in the formula. The platelet count was $490x10^9$/l. Molecular biology analysis confirmed Bcr-Abl positivity; NAP score was 30.The prognostic Socal and Hasford scores implied a low-risk patient. She was treated with hydroxyurea for four years. The treatment with a standard dose (400mg daily) of imatinib mesylate was commenced in 2004. During the treatment some adverse effects were noted: grade (1-2) neutropenia and grade 3 thrombocythopenia. Serial cytogenetic analyses were performed on bone marrow cells by direct preparation approximately every 12 weeks. First cytogenetic analysis was performed two months before the imatinib treatment has been started and in 18 metaphases 18 were Ph` positive t (9; 22). After 3 months with imatinib treatment there wasn't any cytogenetic response, because in 20 metaphases 20 were Ph`positive t (7; 9; 22). After 6 months imatinib treatment cytogenetic analysis revealed the same results in 20 metaphases 19 were Ph`positive. After that the therapy was interrupted due to grade 3 neutropenia for 2 months, and then imatinib treatment was reintroduced at 400mg and maintained. After 12 months cytogenetic analysis revealed the same results, in 20 metaphases 19 were Ph`positive. After 24 months cytogenetic analysis presented new abnormalities with trisomy 8 detected in one Ph`negative cell. Bone marrow did not show any displastic changes at any stage (figure1). In following period patient was still receiving imatinib 400mg daily. According to NCCN and ELN guidelines we should changed the therapy to another second generation TKI inhibitor or allo SCT, but we didn't had any other opportunity for that kind of therapy, only we could administrated imatinib 400mg/day,nither we were able to give 800mg/day. In August 2007 after three years treatment with imatinib, and seven years after diagnose was approached, another disease was noticed: carcinoma planocelulare cutis localized on left hand and fingers, treated with radical surgery. The patient was in chronic phase treated with her only option imatinib 400mg/day until 2012, when the patient died because of thrombi-embolic complication and infection.

DISCUSSION

We present case of a patient with CML in chronic phase, treated with imatinib. This is the first reported instance of karyotype evolution temporally associated with the induction of resistance to imatinib mesylate but without any

signs of evolution of leukemia toward an aggressive form.

Presented patient did not show any clinical and laboratory signs of disease progression despite the appearance of resistance to imatinib and the associated karyotype evolution. She was in stable chronic phase CML more than 10 years after the additional cytogenetic changes have been documented in the Ph-positive cells.

This case is notable, as this patient was in chronic phase and had received a short course of therapy other than imatinib. Could imatinib have influenced the emergence of these abnormal clones?

Patients who have been in late chronic phase, clone abnormalities could be a result of a long disease process or prior therapy negatively inhibiting normal hematopoesis, this providing the selective pressure for the out growth of a resistant Ph`negative clone. Our case, we believe, supports the speculation that imatinib may have a direct effect. The normal Abl gene product is involving in the cellular response to DNA damage; this inhibition may lead to genetic instability (7). Long-term administration of imatinib could have potentially suppressive effects on normal stem cell leading to emergence of new clones. These effects may be more pronounced after long disease duration as the pool of Ph`negative stem cells declines. The patient described did not achieve a major cytogenetic response until 12 months unlike most newly diagnosed patients (8). This may indicate that her disease though in chronic phase was in fact in a letter stage of evolution. Damage to Ph`negative stem cells by previous exposure to cytotoxic agents would add to the risk consistent with our findings (5). The development of chromosomal abnormalities in the Ph-negative metaphases during treatment in patients with CML has been recognized in the past. Before effective therapy for CML was available, treatment with busulphan or hydroxyurea resulted in haematological but not in cytogenetic responses. Thus, this phenomenon could not be evaluated. With IFN-alfa-based therapy, 30-70% of patients achieved a cytogenetic response, which was major in 20-50 %.(9). Fayad et al. (5) first reported the occurrence of cytogenetic abnormalities in the Ph-negative cells in three patients responding to IFN-alfa. One of these patients developed 5q- in one analysis and a complex karyotype in a subsequent analysis, the second developed +18p11, and the third developed deletion 11q21. The first patient developed a myelodysplastic syndrome 86 months later and the other 2 patients remained in complete haematological and cytogenetic response at the time of the report (6 months and 33 months, respectively) after these abnormalities first were noted (5).There are small series in the literature reporting the development of chromosomal abnormalities in Ph-negative cells after imatinib therapy (6). The pathogenesis and clinical significance of these abnormalities is still unclear. To date, all patients reported have been previously treated with chemotherapy (6). Previous treatment with idarubicin and cytosine arabinoside (Ara-C) has been suggested as a risk factor (6). Most patients have been treated with Ara-C in combination with IFN-alfa many years. The majority of patients who have failed to respond to IFN-alfa have received other agents, most frequently homoharringtonine before imatinib became available. Therefore, the role of previous exposure to these agents is difficult to dissect from the exposure to IFN-alfa itself. However, the finding in previously untreated patients and the historic observation in patients treated with IFN-alfa alone (5) suggest that the clonal abnormality may be intrinsic to the primitive haematopoietic stem cell and may not be therapy related. Another important observation is that patients treated with high-dose imatinib (i.e., 800 mg/day) have not developed these abnormalities. Although few patients have so far received the higher doses, it is possible that a faster and more effective elimination of the Ph malignant clone, as noted with high-dose imatinib, (10) may decrease the

risk of development of chromosomal abnormalities in the Ph-negative stem cells. Longer follow-up on a larger population is required to clarify this issue further. Trisomy 8 was particularly common, representing 38% of all abnormalities identified in that study. This abnormality has also been associated with clone evolution (2) C-myc is coded in chromosome 8. Jennings and Mills (11) have suggested a correlation between levels of c-myc and trisomy 8 among patients who developed clone evolution. The significance of this association when trisomy 8 presents in the Ph-negative cells is unclear (12, 13). With a relatively short follow-up, it is clear that these abnormalities can be transient in some patients, even when patients continue in cytogenesis remission. Others show persistence and occasionally increase percentage of these abnormalities. Within the limitations of a small series and a relatively short follow-up period, no prognostic impact can be detected in the duration of cytogenetic remission, transformation to accelerated or blastic phase, or overall survival. Development of true clone evolution occurred in 3 of 21 patients (14%).Cytogenetic abnormalities in the Ph-negative metaphases might appear in some patients with chronic-phase CML who respond to imatinib. This observation highlights the need for close monitoring of patients with CML who receive imatinib. The long-term significance of these abnormalities remains to be determined.

CONCLUSION

The implementations of TKIs in the treatment of CML have changed the management and outcome of this disease. Although good results were obtained with the first-generation TKI, imatinib, the results were not consistent among some patients who developed imatinib resistance or clone evolution. Mutational analysis should be performed in those with imatinib failure, escalating BCR-ABL transcript levels. Mutational data also help in choosing the right second-generation TKI. The introduction of novel therapies may further improve outcomes of CML patients.

ACKNOWLEDGEMENT

Authors acknowledge the great help received from the scholars whose articles cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed. Authors are grateful to IJCRR editorial board members and IJCRR team of reviewers who have helped to bring quality to this manuscript.

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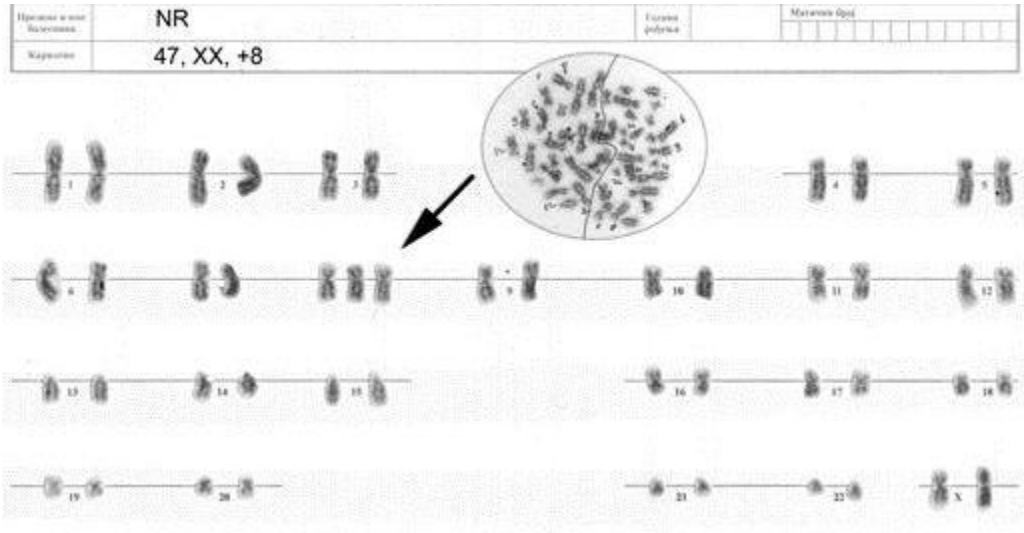

Figure 1-Cariotype of the patient NR, performed after 24 months therapy with Imatin