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Successful Management of a Pregnant Patient With Chronic Myeloid Leukemia Receiving Standard Dose Imatinib

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Abstract. *Background/Aim: As approximately 10% of individuals developing chronic myeloid leukemia (CML) are females aged 20-44 years, a considerable number will consider a planned pregnancy if disease is well controlled by pharmacological treatment. The management of these young patients during pregnancy represents a therapeutic dilemma due to the potential teratogen effects of several tyrosine kinase inhibitors (TKIs) and is a matter of continuous debate. Indeed, despite the existence of several studies, there is currently no consensus on how to manage different pregnancy situations in subjects with CML. Patients and Methods: We describe a female patient diagnosed with Ph-positive CML one month after her first delivery who achieved excellent hematological, cytogenetic and molecular responses while on imatinib mesylate (IM) treatment. Results: The excellent responses allowed the patient to suspend TKI treatment in order to plan a second pregnancy. Despite IM discontinuation, stringent molecular monitoring of her BCR-ABL1/ABL1 levels allowed the safe delivery of the child and, while the patient eventually developed a molecular relapse after four years of treatment discontinuation, upon restarting IM she quickly regained a deep molecular response that is still ongoing. Conclusion: Our case report demonstrates that, if the pregnancy is properly planned in CML patients, it can result in excellent management of the clinical therapeutic option for the benefit of both mother and child.*

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The Philadelphia (Ph) chromosome, generated by the reciprocal translocation of the *BCR* gene at 22q11 and the *ABL1* gene at 9q34, is the cytogenetic culprit of chronic myeloid leukemia (CML) (1-3). At the molecular level, the Ph chromosome generates the *BCR-ABL1* chimeric oncogene encoding for a protein with constitutive tyrosine kinase activity that alters the proliferation rate, survival signaling, immunological interactions and cytoskeleton dynamics of the hematopoietic stem cells (4-8). The development of *BCR-ABL1* tyrosine kinase inhibitors (TKIs) over the past 20 years has significantly improved the outcomes for patients at every stage of Ph+ chromosome CML. Despite these achievements, the emergence of *BCR-ABL1* TKI resistant clones represents a major hurdle for the successful treatment of Ph+ leukemias, requiring often alternative therapeutic approaches (9-13). To data the standard care for chronic-phase CML patients is imatinib mesylate (IM), a semi-specific *BCR-ABL1* TKI. The introduction of IM in clinical practice has dramatically generated unprecedented rates of complete hematological (CHR), cytogenetic (CCyR) and molecular responses (MR) (14-18).

CML accounts for approximately 15% of all adult leukemias with an incidence of about 1 case per 100,000 individuals. Although the median age at diagnosis is 56 years, approximately 17% of cases occur in the range between 20 and 44 years. Therefore, young female CML patients are likely to consider the possibility of giving birth

to one or more children during their lifetime (19, 20). Nevertheless, to date there is still no consensus on how to properly manage pregnancy in female patients with CML. In general, TKI treatment is not recommended during pregnancy due to the teratogen effect of these drugs (21, 22).

In the present report, we describe a patient diagnosed with chronic-phase Ph-positive CML one month after her first delivery who exhibited an optimal response to standard dose IM according to the 2013 European LeukemiaNet recommendations (23). Her excellent molecular response allowed IM discontinuation in order to plan a second pregnancy.

Case Report

In January 2006, a 30-year-old female was referred to our hospital one month after her first delivery with abnormal blood cell counts. At the time, her hemoglobin (Hgb) was 13.2 g/dl with 29.500 white blood cells (WBC) (64% neutrophils, 16% lymphocytes, 4% eosinophils, 3% basophils, 1% monocytes, 6% promyelocytes, 1% metamyelocytes, 4% myelocytes and 1% myeloblasts) and 797.000 platelets (Plt). The spleen was palpable 2 cm below the left costal margin while liver size was normal.

Conventional cytogenetics detected the Ph chromosome in all examined metaphases [karyotype 46, XX, t(9;22)(q34;q11)] and a FISH analysis showed the presence of *BCR-ABL1* in 95% of interphase nuclei. Both conventional cytogenetics and FISH showed chromosome 9 deletion in 30% of the Ph-negative chromosomes examined. Multiplex reverse transcriptase (RT)-PCR detected the e14a2 *BCR-ABL1* transcript (Figure 1A) with an e1a2 *BCR-ABL1* variant barely noticeable by nested RT-PCR. At this time, amplification of the oncogenic transcripts was carried out by Real Time quantitative PCR (Q-PCR) and detected *BCR-ABL1/ABL1* levels of 71.72% (Figure 1B).

Based on these clinical findings the patient was diagnosed with chronic phase CML and was classified as a low Sokal score (24) and low Hasford score (25). Soon thereafter, she began IM 400 mg/day achieving complete hematological and cytogenetic remissions within 3 months and a major molecular response (MR3) after 6 months of IM (*BCR-ABL1/ABL1*^{IS}=0.05050; Figure 1B). Molecular follow up for the e14a2 transcript was continued every 3 months with Q-PCR as previously described (26), while nested RT-PCR was employed for the e1a2 variant with failure to amplify this variant after 6 months of therapy. However, in November 2006 the patient had to suspend IM because of grade II liver toxicity (Aspartate Aminotransferase<200 mU/ml and Alanine Aminotransferase<300 mU/ml). Although, the patient maintained both her CHR and CCyR, we observed an increase of her p210 *BCR-ABL1/ABL1*^{IS} levels (7.512%) (Figure 1B) and the nested RT-PCR successfully not amplified the e1a2 variant. Mutational analysis failed to detect any kinase domain mutations in their Ph-positive clones. Hence, in January 2007 she restarted IM 400 mg/day and after 6 months she achieved a deep molecular response MR^4 (*BCR-ABL1/ABL1*^{IS}=0.00465%) (Figure 1B).

Over the next 4 years, the patient exhibited deep molecular responses varying between MR^4 and MR$^{4.5}$. In July 2011, she approached us wishing to plan a second pregnancy. After careful consideration, we agreed to discontinue IM as long as she would adhere to a strict monthly molecular follow-up as we feared a rapid rise in her oncogenic transcripts after TKI cessation. However, she maintained molecular responses between MR^4 and MR4.5 even in the absence of IM (Figure 1B) and, at 38 weeks (April 2012), delivered *via* cesarean section a healthy baby girl (weight 2,92 kg; height 48 cm; APGAR 9). As her MR^4 was stable after giving birth to her second child, she decided to prolong IM discontinuation and remained TKI-free until January 2015 when she lost her major molecular response (*BCR-ABL1/ABL1*^{IS}=0.12534%; Figure 1B). At this time, she restarted IM and, after 6 months, again attained an MR^4 that is ongoing at the present time.

Total RNA was extracted from peripheral blood or bone marrow leucocytes, using the RNeasy mini kit (Qiagen, Hilden, Germany), according to the manufacturer's protocol. cDNA synthesis was carried out using Moloney Murine Leukemia Virus Reserve Transcriptase (Life Technologies, Carlsbad, CA, USA). Cytogenetic analysis performed by G-banding (27) and FISH analysis carried out as previously reported (28). The detection of different *BCR-ABL1* fusion transcripts was performed using multiplex reverse transcriptase protocol able to identify contemporary multiplex *BCR-ABL1* isoforms (29, 30).

The e14a2 *BCR-ABL1* fusion transcripts were quantified by Q-PCR according to the suggested recommendations (31) and molecular analysis was performed as previously reported (32). Mutation analysis of the ABL kinase domain by clonal sequencing was performed as previously described (33).

Informed Consent

Informed consent was received from the patient for the publication of the report as specified in the Declaration of Helsinki.

Discussion and Conclusion

Pregnancy management in female patients diagnosed with chronic phase CML is a matter of debate and represents a therapeutic dilemma due to the potential teratogen effects of different TKIs. Indeed, several studies have highlighted the risk of embryo-fetal toxicity caused by some *ABL1* kinase inhibitors resulting in skeletal malformations, spontaneous abortion, and fetal growth restriction (34, 35).

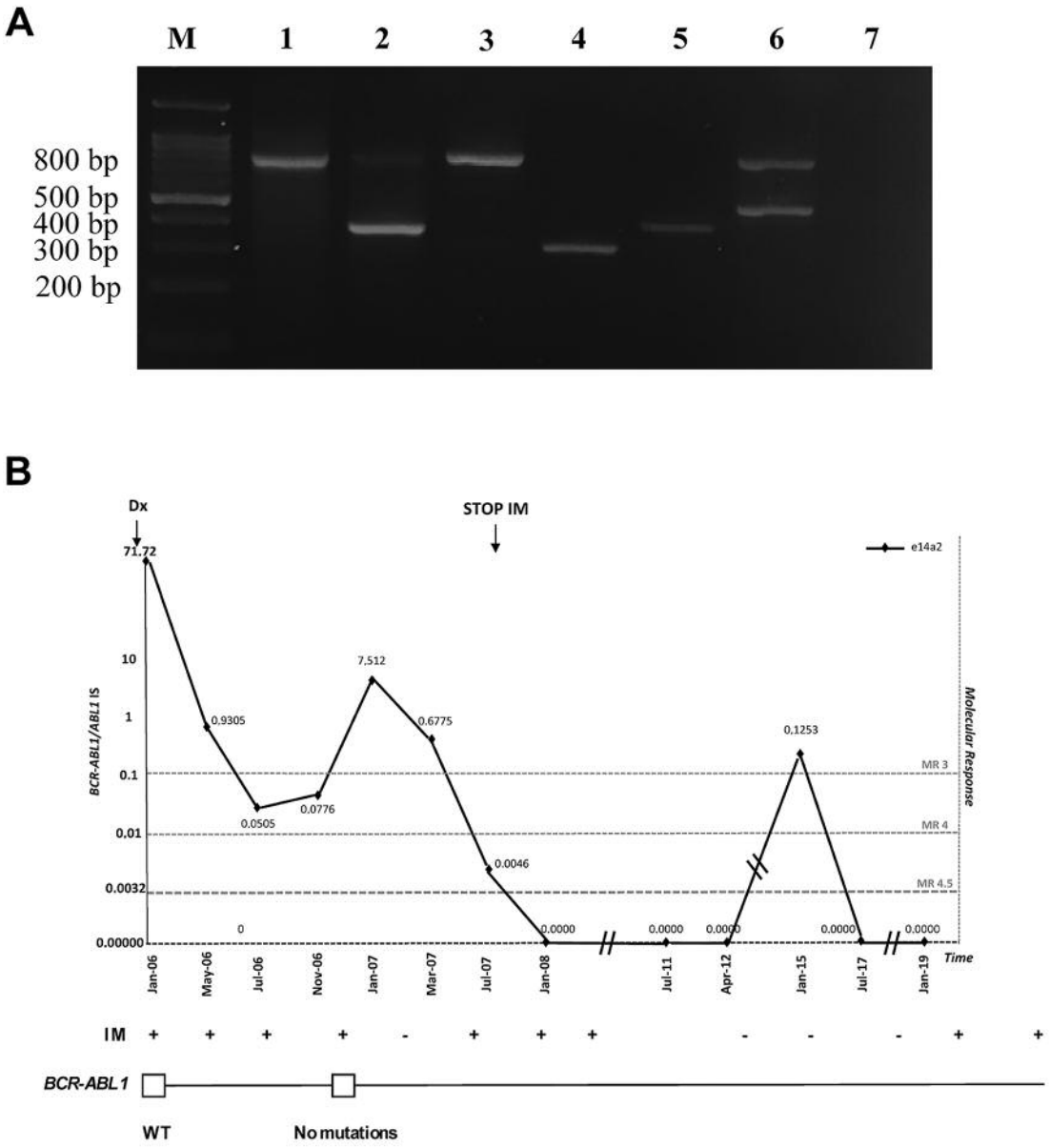

Figure 1. *A. Multiplex RT-PCR analysis of the different BCR-ABL1 fusion transcripts. Lane M: Molecular size marker (100-bp ladder); lane 1: patient negative for CML; lane 2: e14a2 (385 bp) from patient; lane 3: patient negative for CML; lane 4: e13a2 (310 pb) positive control; lane 5: e14a2 positive control; lane 6: e1a2 positive control; lane 7: negative control. B. Molecular response to IM. Monitoring of patient's disease evolution indicates variations in e14a2 transcripts and drug treatment (top panel) or BCR-ABL1 mutant clones (middle panel). Dotted lines represent achievement of a major (MR3) or a deep molecular response (MR4; MR4.5). A white square indicates wild-type BCR-ABL1. IM: Imatinib.*

At the present time, there are no consensus guidelines regarding the management of a pregnancy in CML patients. Experts in the field are only suggest that female subjects still in their reproductive age should be informed about the risks of an unintended pregnancy during TKI therapy and be encouraged to carefully discuss family planning with their physician. A pregnancy should be considered after achieving durable and complete cytogenetic responses followed by equally enduring major molecular responses for at least 18-24 months (20, 34). Under these circumstances, TKI therapy should be discontinued shortly before ovulation and *BCR-ABL1/ABL1* levels should be monitored on a monthly basis (34, 35). In case of cytogenetic or hematological relapses occurring during pregnancy, each physician will have to

evaluate patient clinical history, rapidity of disease relapse and pregnancy status (period of gestation) in order to advise the mother as to the most appropriate way to proceed.

In this study, we report the case of a female patient diagnosed with CML that rapidly achieved hematologic, cytogenetic, and molecular responses on IM treatment and therefore wanted to consider a second pregnancy. Several reports have shown that women with CML can successfully deliver healthy babies with careful planning and strict disease monitoring.

In our case, the decision to discontinue TKI therapy was further supported by recent findings indicating that patients who achieve and maintain a deep molecular response (≥MR4) may be considered for TKI discontinuation as they could remain in treatment-free remission (TFR) even after drug cessation. Indeed, TFR is an attractive possibility for all CML patients as it often provides significant relief from TKI toxicities and general improvements in quality-of-life (36, 37). TFR is now considered for many young patients affected by CML and also an end point for some clinical trials. We think that the optimal management of pregnancy in CML is another good reason for pursuing clinical studies aimed to find the best way to manage TFR.

In the last eighteen years, TKIs have radically transformed the management of CML that usually becomes a lifelong chronic condition. However, the management of a planned pregnancy in CML patients requires a thorough evaluation of both risks and benefits that should be carefully discussed between the patient and her physician. To avoid potential teratogenicity to the fetus, it is necessary to find a balance between the mother's childbearing desire and the optimal pharmacological treatment required by the disease. Our case report demonstrated that, if the pregnancy is properly planned, it can result in excellent outcomes for both the mother and child.

Conflicts of Interest

The Authors declare that they have no competing interests regarding this study.

Authors' Contributions

SS, ET and MM designed and performed the experiments; SS, ET, MM, SRV, MSP, AP CR and SDR analyzed and interpreted the data; SS wrote the paper; SR, FS, FDR, CM and LM made a critical revision of paper; LM conceived the original idea and supervised the project.

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