Safety of Imatinib During Pregnancy: Report of Two Cases and Review of Literature

Gebelikte İmatinib Kullanımının Güvenliği: İki Olgu Sunumu ve Literatürün Gözden Geçirilmesi

Özlem ŞAHİN BALÇIK, MD,[a]
İlknur İNEGÖL GÜMÜŞ, MD,[b]
Zeynep KAMALAK, MD,[b]
Handan CİPİL, MD,[a]
İkbal KAYGUSUZ, MD,[b]
Ali KOŞAR, MD[a]

Departments of
[a]Hematology,
[b]Obstetrics and Gynecology,
Fatih University Faculty of Medicine,
Ankara

Geliş Tarihi/*Received:* 28.05.2010
Kabul Tarihi/*Accepted:* 20.07.2010

Yazışma Adresi/*Correspondence:*
İlknur İNEGÖL GÜMÜŞ, MD
Fatih University Faculty of Medicine,
Department of
Obstetrics and Gynecology,
Ankara,
TÜRKİYE/TURKEY
ilknurinegol@yahoo.com

ABSTRACT Imatinib that first administered to patients with chronic myeloid leukemia (CML) in June 1998 is a potent inhibitor of tyrosine kinase used in the treatment of with positive Philadelphia chromosome CML, acute lymphoblastic leukemia and gastrointestinal stromal tumors (GISTs). In recent years pregnant women exposed to imatinib are observed more frequently, because of increasing the survival of the patients diagnosed with CML and GISTs during the reproductive age. Owing to its teratogenic effects demonstrated in the animal trials, imatinib is not recommended in pregnant or during the reproductive age, and an effective contraception is recommended to the reproductive women undergoing to the treatment. Due to use imatinib during pregnancy, few abortuses and various congenital anomalies are noted along with successful singleton and multiple pregnancies. The pregnancy of a patient with a chronic myeloid leukemia requiring treatment presents a dilemma, both to the physician and to the patient. Therefore, the potential risks must be considered carefully, when deciding imatinib therapy for pregnant and lactating women. In this paper, we reported two cases who were exposed to imatinib in first trimester of their pregnanc and gave a birth with inguinal hernia and the other gave a healthy baby. We also discussed the safety and the effects of imatinib during pregnancy and lactation period for mother and fetus.

Key Words: Imatinib; pregnancy; leukemia, myelogenous, chronic, BCR-ABL positive

ÖZET İlk olarak Haziran 1998 yılında kullanılmaya başlanan imatinib, Philadelphia kromozomu pozitif olan kronik miyeloid lösemi (KML), akut lemfositik lösemi ve gastrointestinal stromal tümörler (GIST)'de kullanılan güçlü bir tirozin kinaz inhibitörüdür. Son yıllarda üreme yaş grubunda da KML ve GIST'lerde artış olduğundan imatinibe maruz kalan gebe sayısı da artmıştır. Hayvan çalışmalarında teratojenik etkileri gösterildiğinden gebelikte kullanımı önerilmemekte ve reprodüktif dönemde tedavi altında olanlara etkili bir korunma yöntemi tavsiye edilmektedir. Bazı çalışmalarda gebelik sırasında imatinib kullanımına bağlı tek ve çoğul gebeliklerde bazı düşük ve değişik konjenital anomaliler rapor edilmiştir. KML'li gebenin tedavi gerekliliği hem doktor hem de hasta için zor bir durumdur. Bu yüzden gebelikte imatinib kullanılmasına karar verildiği zaman potansiyel riskleri göz önünde bulundurulmalı, takipler dikkatlice yapılmalıdır. Bu yazımızda gebeliği sırasında 1. trimesterde imatinibe maruz kalan, biri sağlıklı, diğeri sağlıklı gebeliğini takiben inguinal fıtık tespit edilen bebek doğuran iki olgumuzu sunduk ve gebelik sırasında imatinib kullanımının hem anne hem de fetüs açısından güvenliğini ilgili literatürler ışığında tartıştık.

Anahtar Kelimeler: İmatinib; gebelik; lösemi, miyeloid, kronik, BCR-ABL pozitif

Turkiye Klinikleri J Gynecol Obst 2010;20(6):387-91

Pregnancy is a long and risky journey and the pregnancy of a patient with a neoplastic disease gets it more critical and indeterminate for mother and fetus and their family. Hemotological malignancies are common malignancies diagnosed during pregnancy. Chronic myeloid leu-

kemia (CML) constitutes less than 10% of leukemias in pregnancy with estimated incidence of one in 75.000-100.000 pregnancies.[1]

Imatinib that first administered to patients with CML in June 1998 is a potent inhibitor of tyrosine kinase used in the treatment of with positive Philadelphia chromosome (CML), acute lymphoblastic leukemia and gastrointestinal stromal tumors (GISTs).[2-4] Due to the increase in the survival of the patients diagnosed with CML and GISTs during the reproductive age, pregnant women exposed to imatinib are observed more frequently. Owing to its teratogenic effects demonstrated in the animal trials, imatinib is not recommended in pregnancy or during reproductive age, and an effective contraception is recommended to the reproductive women undergoing to the treatment.[5]

Few abortuses and various congenital anomalies are noted along with successful singleton and multiple pregnancies.[6-11] The pregnancy of a patient with a CML requiring treatment presents a dilemma, both to the physician and to the patient. Therefore, the potential risks must be considered carefully, when deciding imatinib therapy for pregnant and lactating women.

Here we discussed the safety and the effects of imatinib during pregnancy and lactation period according to the related articles.

CASE REPORTS

CASE 1

Twenty one-year-old women, diagnosed with Philadelphia (Ph) chromosome-positive chronic phase CML, was entered into imatinib treatment. Complete hematologic remission and major molecular remission, respectively, were attained during the 1st and 6th months of imatinib treatment. Gestation was determined during the 9th month of treatment. She was being exposed to imatinib at a dose of 400 mg/day for 6 weeks, beginning from gestation. She was taken into follow-up without medication once gestation was determined. Chronic phase CML recurred in this subject two months after medication was terminated. The subject did not want to use medication. She has not been given any treatment during gestation. Her leukocyte count was 239 x 10^9/L, when gestation completed via normal vaginal delivery at week 39. Her peripheral blood smear was consistent with chronic phase CML. The newborn was normal. Imatinib treatment was restarted for this subject following delivery and complete hematologic response was achieved again after one month. Now, the infant is 6 months old without any health problem.

CASE 2

A 23-year-old women, diagnosed with Ph chromosome-positive chronic phase CML, was entered into imatinib treatment. Complete hematologic remission and major molecular remission, respectively, were attained at the 2nd and 6th months of imatinib treatment. Gestation was determined at the 12th month of treatment. She was being exposed to imatinib at a dose of 400 mg/day for 5 weeks, beginning from gestation. She was taken into follow-up without medication once gestation was determined. Complete hematologic response kept continuing throughout gestation. The baby was born via normal vaginal delivery. The newborn was diagnosed with congenital unilateral inguinal hernia. The infant underwent inguinal hernia surgery at 3 months of age. Imatinib treatment was commenced following delivery, still without any clinical or laboratory evidence of pathology during the 5th month of treatment.

Chronic Myeloid Leukemia and Pregnancy

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder that occurs as a result of a reciprocal translocation between chromosome 22 and chromosome 9, or the Philadelphia translocation.[12] This translocation createsa fusion gene-breakpoint cluster region bcr-abl protooncogene, which encodes an oncoprotein that has constitutivelyactive abl tyrosine kinase (TK) activity. The introduction of the TK inhibitor (TKI) imatinib in 1998 indisputably advanced the clinical management of cancer.[13]

The management of leukaemia in pregnancy needs an interdisciplinary approach and a careful

monitoring of the pregnancy until delivery. Treatment should be avoided in the first trimester. The prognosis of pregnant women with acute leukaemia corresponds to that of an age-matched and diagnosis-matched non-pregnant cohort of patients, provided appropriate treatment is given. If given as of the second trimester, the typical chemotherapy regimes used for acute leukaemias imply acceptable acute toxicities to the fetus, with a somewhat increased risk of premature birth or developmental retardation, but no clear evidence of late sequelae in children and adolescents who were exposed to cytostatic agents whilst in utero.[14] In CML targeted therapy with imatinib mesylate is safe as of the second trimester, and possibly even before. Obstetric care and monitoring of women with leukaemia are essential throughout the pregnancy to ensure the best possible outcome for mother and child.[14]

Imatinib and Pregnancy

Imatinib has demonstrated its efficacy by increasing overall survival and substantially improving the life expectancyand quality of life of patients with CML. As a result,patients who are of childbearing age and are currently being treated with imatinib now find themselves contemplating reproductive opportunities that would not have otherwise been possible. However, the occurrence of CML during pregnancy poses a unique clinical challenge for physicians treating these patients and requires balancing concerns between maternal survival and fetal health in both the short- and long-term. Because imatinib was teratogenic in rats, it was strongly advised that effective contraceptionbe used during therapy to prevent pregnancy.[15]

Due to the increase in the survival of the patients diagnosed with CML and GISTs during the reproductive age, pregnant women exposed to imatinib are observed.[6-11,16] In the trials performed with the patients undergoing pregnancy during the treatment with imatinib, the frequency of abortus was found to be low and normal termination was seen in most of the pregnancies.[10,11] Congenital abnormalities including hypospadias, small intestinal rotation, meningocele, hydrocephaly, cleft palate, polydactyly, renal agenesis are observed in a rate of 10%.[10,11] Three of them were similar complex malformations with undefined causes.[11] Despite it is demonstrated that imatinib can pass through the immature placenta, congenital anomalies were not obtained in some babies that underwent imatinib therapy during second and third trimester or during the lactation, according to literature.[1,8,17,18] Administration of imatinib is recommended to be discontinued during lactation period, for the reason that imatinib and its active metabolite CGP74588 are determined in the milk.[18] Similarly, it is estimated in a study condemned in rats that a new tyrosine kinas inhibitor, dasatinibin, is also determined in the milk.[19] No abnormality was observed in the babies of the cases who became father when receiving imatinib.[20,21] A healthy infant was delivered by a patient who became pregnant while undergoing the treatment of a new generation tyrosine kinas, nilotinib.[13] Imatinib was discontinued in most of the cases that became pregnant while receiving imatinib.[7,17,22] Some of the cases were followed up without any treatment owing to the fact that hematologic and molecular responses are continuing until the pregnancy and the lactation periods end up, and interferon and leukoforesis were administered to some cases due to hematologic relapse.[7,17,22] While the imatinib response continue in some of the cases restarted to receive imatinib following the pregnancy and the lactation periods, some of the cases were switched to another tyrosine kinas inhibitor due to the resistance to the imatinib therapy.[17,22] There is not sufficient number of cases to state that interrupting imatinib therapy during pregnancy may lead to refractory disease (Table 1).

Imatinib in Breast Milk

There are various conflicting evidences about imatinib in breastfeeding. According to Kronenberger's results breastfeeding cannot be recommended during treatment with imatinib.[23] They found that found that the level of imatinib in breast milk was about half the plasma level. The active metabolite NDesM-IM accumulated about threefold in breast milk as compared to plasma levels.[23]

TABLE 1: Imanitib therapy during pregnancy.

References	Study Design	Exposure to imatinib	Adverse Congenital malformations	outcomes Abortions	Preterm delivery	Healthy infants (n)
Hensley et al (2003)[15]	Case series (26)	First and second trimester	Hypospadias:1	elective:11 pontaneous:5		2
Sotiropoulos et al (2004)[25]	2 presented cases	First and second trimester	__		Delivery at 26 weeks both died	0
Prabhash et al (2005)[26]	2 presented cases	Throughout pregnancy	__	__	__	2
Ault et al (2005)[10]	Case series (10)	First trimester	Hypospadias:1	elective:1 spontaneous:2		8
Al Kindi et al (2005)[27]	3 presented cases	Throughout pregnancy	__	1	__	2
Koh et al (2006)[28]	1 presented case	First trimester	__	__	__	1
Choudhary et al (2006)[29]	1 presented case	First trimester	Fatal meningocele, dead fetus	1	__	0
Suppiah et al (2006)[30]	1 presented case	First trimester	__	__	__	1
Yilmaz et al (2007)[31]	3 presented cases	Throughout pregnancy	__	__	__	3
Russell et al (2007)[18]	2 presented cases	First and third trimester	__	__	__	2
Garderet et al (2007)[9]	2 presented cases	First trimester	__	__	__	2
Dolai et al (2008)[22]	1 presented case		__	__	__	1
Skoumalova et al (2008)[32]	1 presented case	First trimester	__	__	__	1
Sora et al (2008)[33]	1 presented case	First trimester	__	__	__	1
Meera et al (2008)[7]	1 presented case (twin)	First trimester	__	__	__	2
Pye et al (2008)[11]	Case series (180)	Throughout pregnancy	pyloric stenosis:1 hypospadias:2 Complicated anomaly:9	elective:35 spontaneous:18	__	63
Buyukbayrak et al (2008)[17]	1 presented case	Second and third trimester	__	__	__	1
Tsuzuki M (2009)[5]	1 presented case	First trimester				1
Scherjon et al (2009)[16]	1 presented case	First trimester	__	__	__	1
Ali R et al (2009)[8]	1 presented case	Second and third trimester	__	__	__	1

Carlo et al reported a case with a CML woman used imatinib during breastfeeding.[24] They suggested that mothers with CML could safely breast-feed their children. But, the effects of even low-dose, chronic exposure of infants to imatinib are not known Given the important biologic and psychological value of breast-feeding, such information will be useful for CML patients considering a pregnancy and for the hematologists caring for them. They concluded that case mothers should discuss this option with their pediatrician.[24] And Ali et al noted that breast feeding during imatinib therapy seems to be safe; but, the efects of chronic infant exposure to imatinib are not known.[8]

To conclude, it seems continuing to be a dilemma for treating CML in pregnancy with imatinib safety for mother and fetus. We think that an effective contraception method should be recommended to the women in reproductive age during the imatinib therapy. The potential risks must be considered when deciding imatinib therapy in patients in the pregnancy or lactation period.

REFERENCES

1. Klamová H, Marková M, Moravcová J, Siskóvá M, Cetkovský P, Machová Poláková K. Response to treatment in women with chronic myeloid leukemia during pregnancy and after delivery. Leuk Res 2009;33(11):1567-9.
2. Fava C, Cortes J. Optimizing first-line therapy for patients with chronic myeloid leukemia. Semin Hematol 2009;46(2 Suppl 3):S5-10.
3. Ottmann OG, Pfeifer H. Management of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Hematology Am Soc Hematol Educ Program 2009:371-81.
4. Reichardt P, Blay JY, Mehren M. Towards global consensus in the treatment of gastrointestinal stromal tumor. Expert Rev Anticancer Ther 2010;10(2):221-32.

5. Tsuzuki M, Inaguma Y, Handa K, Hasegawa A, Yamamoto Y, Watanabe M, et al. Successful pregnancy in a patient with chronic myeloid leukemia under treatment with imatinib. Intern Med 2009;48(16):1433-5.
6. Cole S, Kantarjian H, Ault P, Cortés JE. Successful completion of pregnancy in a patient with chronic myeloid leukemia without active intervention: a case report and review of the literature. Clin Lymphoma Myeloma 2009;9(4): 324-7.
7. Meera V, Jijina F, Shrikande M, Madkaikar M, Ghosh K. Twin pregnancy in a patient of chronic myeloid leukemia on imatinib therapy. Leuk Res 2008;32(10):1620-2.
8. Ali R, Ozkalemkas F, Kimya Y, Koksal N, Ozkocaman V, Gulten T, et al. Imatinib use during pregnancy and breast feeding: a case report and review of the literature. Arch Gynecol Obstet 2009;280(2):169-75.
9. Garderet L, Santacruz R, Barbu V, van den Akker J, Carbonne B, Gorin NC. Two successful pregnancies in a chronic myeloid leukemia patient treated with imatinib. Haematologica 2007;92(1):e9-10.
10. Ault P, Kantarjian H, O'Brien S, Faderl S, Beran M, Rios MB, et al. Pregnancy among patients with chronic myeloid leukemia treated with imatinib. J Clin Oncol 2006;24(7):1204-8.
11. Pye SM, Cortes J, Ault P, Hatfield A, Kantarjian H, Pilot R, et al. The effects of imatinib on pregnancy outcome. Blood 2008;111(12): 5505-8.
12. Rowley JD. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 1973;243(5405): 290-3.
13. Conchon M, Sanabani SS, Bendit I, Santos FM, Serpa M, Dorliac-Llacer PE. Two successful pregnancies in a woman with chronic myeloid leukemia exposed to nilotinib during the first trimester of her second pregnancy: case study. J Hematol Oncol 2009;2:42.
14. Fey MF, Surbek D. Leukaemia and pregnancy. Recent Results Cancer Res 2008;178: 97-110.
15. Hensley ML, Ford JM. Imatinib treatment: specific issues related to safety, fertility, and pregnancy. Semin Hematol 2003;40(2 Suppl 2): 21-5.
16. Scherjon S, Lam WF, Gelderblom H, Jansen FW. Gastrointestinal stromal tumor in pregnancy: a case report. Case Report Med 2009;2009:456402.
17. Buyukbayrak EE, Ergen B, Karsidag YK, Kars B, Turan C, Argon D. Pregnancy complicated with chronic myelogeneous leukemia (CML) successfully treated with imatinib: a case report. Arch Gynecol Obstet 2008;278(2):161-3.
18. Russell MA, Carpenter MW, Akhtar MS, Lagattuta TF, Egorin MJ. Imatinib mesylate and metabolite concentrations in maternal blood, umbilical cord blood, placenta and breast milk. J Perinatol 2007;27(4):241-3.
19. He K, Lago MW, Iyer RA, Shyu WC, Humphreys WG, Christopher LJ. Lacteal secretion, fetal and maternal tissue distribution of dasatinib in rats. Drug Metab Dispos 2008;36(12): 2564-70.
20. Breccia M, Cannella L, Montefusco E, Frustaci A, Pacilli M, Alimena G. Male patients with chronic myeloid leukemia treated with imatinib involved in healthy pregnancies: report of five cases. Leuk Res 2008;32(3):519-20.
21. Ramasamy K, Hayden J, Lim Z, Mufti GJ, Ho AY. Successful pregnancies involving men with chronic myeloid leukaemia on imatinib therapy. Br J Haematol 2007;137(4):374-5.
22. Dolai TK, Bhargava R, Mahapatra M, Mishra P, Seth T, Pati HP, et al. Is imatinib safe during pregnancy? Leuk Res 2009;33(4):572-3.
23. Kronenberger R, Schleyer E, Bornhäuser M, Ehninger G, Gattermann N, Blum S. Imatinib in breast milk. Ann Hematol 2009;88(12): 1265-6.
24. Gambacorti-Passerini CB, Tornaghi L, Marangon E, Franceschino A, Pogliani EM, D'Incalci M, et al. Imatinib concentrations in human milk. Blood 2007;109(4):1790.
25. Sotiropoulos D, Adamidou D, Athanasiadou A, Goulis DG, Fassas A, Anagnostopoulos A. Two pregnancies resulting in a healthy newborn in a CML patient treated with imatinib. Blood 2004;104(11): 4694.
26. Prabhash K, Sastry PS, Biswas G, Bakshi A, Prasad N, Menon H, et al. Pregnancy outcome of two patients treated with imatinib. Ann Oncol 2005;16(12):1983-4.
27. AlKindi S, Dennison D, Pathare A. Imatinib in pregnancy. Eur J Haematol 2005;74(6):535-7.
28. Koh LP, Kanagalingam D. Pregnancies in patients with chronic myeloid leukemia in the era of imatinib. Int J Hematol 2006;84(5):459-62.
29. Choudhary DR, Mishra P, Kumar R, Mahapatra M, Choudhry VP. Pregnancy on imatinib: fatal outcome with meningocele. Ann Oncol 2006;17(1):178-9.
30. Suppiah R, Kalaycio M. Successful outcome of pregnancy in a patient with chronic myelogenous leukemia exposed to imatinib during the first trimester. Leuk Lymphoma 2006;47 (6):1149-50.
31. Yilmaz M, Demirhan O, Kuçukosmanoglu E, Pehlivan M, Okan V, Balat O, et al. Pregnancy in patients with chronic myeloid leukemia treated with imatinib. Leuk Lymphoma 2007;48 (12):2454-6.
32. Skoumalova I, Vondrakova J, Rohon P, Rozmanova S, Jarosova M, Indrak K, et al. Successful childbirth in a patient with chronic myelogenous leukemia treated with imatinib mesylate during early pregnancy. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2008;152(1):121-3.
33. Sorà F, De Matteis S, Bajer J, D'alò F, Leone G, Sica S. Persistence of molecular remission throughout pregnancy in CML after imatinib. Leuk Res 2009;33(6):e6-7.