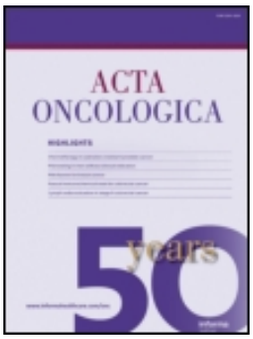

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: informahealthcare.com/journals/ionc20

Fatherhood during imatinib

Emad Shash, Simona Bassi, Emilia Cocorocchio, Giovanni Maria Colpi, Saverio Cinieri & Fedro Alessandro Peccatori

To cite this article: Emad Shash, Simona Bassi, Emilia Cocorocchio, Giovanni Maria Colpi, Saverio Cinieri & Fedro Alessandro Peccatori (2011) Fatherhood during imatinib, Acta Oncologica, 50:5, 734-735, DOI: 10.3109/0284186X.2011.577562

To link to this article: https://doi.org/10.3109/0284186X.2011.577562

Published online: 26 Apr 2011.

Acta Oncologica, 2011; 50: 734–735

informa
healthcare

LETTER TO THE EDITOR

Fatherhood during imatinib

EMAD SHASH[1,2], SIMONA BASSI[2], EMILIA COCOROCCHIO[2], GIOVANNI MARIA COLPI[3], SAVERIO CINIERI[4] & FEDRO ALESSANDRO PECCATORI[2,5]

[1]*Department of Medical Oncology, National Cancer Institute, Cairo University, Cairo, Egypt,* [2]*Department of Medicine, Division of Hemato-Oncology, European Institute of Oncology, Milano, Italy,* [3]*Andrological Urology Unit and IVF Center, S Paolo Hospital, University of Milan, Milano, Italy,* [4]*Division of Medical Oncology, A Perrino Hospital and European Institute of Oncology, Brindisi and Milan, Italy and* [5]*Fertility and Pregnancy in Oncology Project, European Institute of Oncology, Milano, Italy*

To the Editor,

Imatinib mesylate has dramatically improved the prognosis of chronic myeloid leukemia (CML) patients with an estimated six years overall survival of 88% [1]. More than 50% of all CML patients are males and 45.8% are diagnosed between 20 and 64 years of age [2], but no clear data about the potential gonadotoxicity and the possible harmful effects on offspring of imatinib are available.

Imatinib is a small-molecular analog of ATP that inhibits the tyrosine kinase activities of Bcr-Abl, PDGFR-α, PDGFR-β, c-Fms, Arg and c-kit [3]. In rodents, c-kit and its ligand SCF play an essential role in testicular development regulating germ cells migration, proliferation and survival. In addition, PDGF is a central mediator in the maturation of Leydig cells [4]. Accordingly, inhibition of these developmental signaling pathways could have adverse effects on normal sperm and testosterone production. Here, we report the case of a 36-year-old patient diagnosed with CML in November 2006 who fathered twice while on imatinib at the dosage of 400 mg/day. Conceptions occurred after one month and 22 months from therapy start, respectively. Both pregnancies were normal and without complications, and both female babies were delivered at term by vaginal deliveries. Birth weights and lengths were within the 95th percentiles and subsequent development was within normal ranges. The patient obtained a complete cytogenetic and molecular response after four months of therapy and is still in complete molecular response after 48 months from diagnosis.

Animal studies investigating the effects of imatinib on gonadal function showed that when prepubertal male rats were exposed to 150 mg/kg of imatinib for three days, there was severe impairment of gonocyte migration, spermatogonial stem cell proliferation and Leydig cell maturation. By the age of 11 weeks, the exposed animals had normal epididymal sperm counts although follicle stimulating hormone (FSH) and luteinising hormone (LH) remained above normal levels [5]. In another preclinical study, adult male rats received 60 mg/kg for 70 days prior to mating. They had testicular and epididymal duct shrinkage with low sperm count, which was not seen at doses ≤20 mg/kg. Nonetheless, fertility was not affected and this was confirmed also in the first generation offspring [3].

Hensley and Ford were the first to report the outcomes of 18 pregnancies among partners of men treated with imatinib. Later on, 20 other pregnancies were reported, summing up to 40 pregnancies, including the two described here. Three miscarriages, two induced abortions and one gut malrotation of 40 pregnancies were reported. Patients characteristics and pregnancies outcome are illustrated in Table I [6–10]. Two case reports describe oligospermia after imatinib treatment. In the first one, the patient received high dose (800 mg/day) imatinib since adolescence for hypereosinophilic syndrome [11]. In the second one, the patient developed oligo-azoospermia when 18 years old after prolonged imatinib administration (400 mg/day) for CML started at 11 years of age [12].

Animal and human data suggest that prolonged exposure to imatinib could be associated with low sperm count, even if this may not affect fertility as demonstrated by the reported cases. Nonetheless, patients should be counselled about the possibility that azoospermia might eventually occur and should be encouraged to bank their sperm either before or during

Correspondence: Fedro Alessandro Peccatori, Department of Medicine, Division of Haemato-Oncology, Fertility & Pregnancy in Oncology Project, Istituto Europeo di Oncologia, Via Ripamonti 435, 20141 Milan, Italy. Tel: +39 257489538. Fax: +39 294379241. E-mail: fedro.peccatori@ieo.it

(Received 22 March 2011; accepted 29 March 2011)

ISSN 0284-186X print/ISSN 1651-226X online © 2011 Informa Healthcare
DOI: 10.3109/0284186X.2011.577562

Table I. Outcome of reported pregnancies for males under imatinib therapy.

Authors	Number of reported pregnancies	Median age at time of conception/Range	Median exposure period to Imatinib at time of Conception / Range	Median dose of Imatinib	Complications/ Miscarriage	Delivery
Hensley & Ford ° [6]	18	NA	NA	400–800 mg/day	(2) Miscarriage (2) Abortion	(4) Successful delivery (6) Ongoing at time of reporting (4) No available data
Ault et al. [7]	8	35 years/26–38 years	20 ms/1–30 ms	700 mg/day	(1) Miscarriage (1) born with gut rotation	(3) VD (4) CS
Ramasamy et al. [8]	5	45 years/41–46 years	18 ms/4–48 ms	600 mg/day	No	(4) VD (1) CS
Breccia et al. [9]	5	37 years/26–43 years	16 ms/6–31 ms	400 mg/day	(1) Threatened miscarriage	(4) VD (1) CS
Pacilli et al. [10]	2	39 years & 46 years	16 ms & 23 ms	400 mg/day	No	(1) VD (1) CS
Shash et al.	2	36 years & 38 years	1 ms & 22 ms	400 mg/day	No	(2) VD

NA, Not Available; VD, Vaginal Delivery; CS, Caesarean Section.
°No available data regarding the ongoing pregnancies outcome reported in the paper.

therapy. Even if data are limited, imatinib therapy does not seem to be associated with major fetal complication when conception occurred during the treatment of the male partner. However, prolonged follow-up of the offspring and specific studies on sperm integrity and testosterone production are warranted.

Acknowledgements

Emad Shash was supported by the "Clinical Unit Visit Fellowship" of the European Society of Medical Oncology (ESMO).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Marin D. Current Status of imatinib as frontline therapy for chronic myeloid leukemia. Semin Hematol 2010;47:312–8.
[2] National Cancer Institute [Internet]. Surveillance Epidemiology and End Results. US incidence and survival SEER 2003–2007 [accessed 2010 Nov]. Available from: http://www.seer.cancer.gov
[3] Novartis Pharmaceuticals Corporation [Internet]. Available from: www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf
[4] Mariani S, Basciani S, Arizzi M, Spera G, Gnessi L. PDGF and the testis. Trends Endocrinol Metab 2002;13:11–7.
[5] Nurmio M, Toppari J, Zaman F, Andersson AM, Paranko J, Soder O, et al. Inhibition of tyrosine kinases PDGFR and C-Kit by imatinib mesylate interferes with postnatal testicular development in the rat. Int J Androl 2007;30:366–76.
[6] Hensley ML, Ford JM. Imatinib treatment: Specific issues related to safety, fertility, and pregnancy. Semin Hematol 2003;40(Suppl 2):21–5.
[7] Ault P, Kantarjian H, O'Brien S, Faderl S, Beran M, Rios MB, et al. Pregnancy among patients with chronic myeloid leukaemia treated with imatinib. J Clin Oncol 2006;24:1204–8.
[8] 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;137:374–5.
[9] 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;32:519–20.
[10] Pacilli M, Montefusco E, Porrini R. Conception of healthy children under Imatinib treatment in two men affected by chronic myeloid leukaemia. Hematologica 2009;94(Suppl 4):168–9. (Abstract) 42nd Congress of Italian Society of Haematology.
[11] Seshadri T, Seymour JF, McArthur GA. Oligospermia in a patient receiving imatinib therapy for the hypereosinophilic syndrome. New Engl J Med 2004;351:2134–5.
[12] Mariani S, Basciani S, Fabbri A, Agati L, Ulisse S, Lubrano C, et al. Severe oligozoospermia in a young man with chronic myeloid leukemia on long term treatment with imatinib started before puberty. Fertil Steril Epub 2010 Oct 1. doi:10.1016/j.fertnstert.2010.08.060 (PMID: 20888557).