The effects of imatinib on pregnancy outcome

Seonaid M. Pye,[1] Jorge Cortes,[2] Patricia Ault,[2] Alan Hatfield,[3] Hagop Kantarjian,[2] Richard Pilot,[3] Gianantonio Rosti,[4] and Jane F. Apperley[1]

[1]Department of Haematology, Division of Investigative Science, Imperial College, London, United Kingdom; [2]University of Texas M. D. Anderson Cancer Center, Houston; [3]Novartis Pharmaceuticals, East Hanover, NJ; and [4]Institute of Hematology and Medical Oncology Seràgnoli, Bologna, Italy

Imatinib has now been in use for almost 10 years. Despite this cumulative experience, little is known about its effects on pregnancy; as a result, there are few published data to facilitate the counseling of women who conceive while taking imatinib. The results we now present provide information which may be of use in such circumstances. Of 180 women exposed to imatinib during pregnancy, outcome data are available for 125 (69%). Of those with known outcomes, 50% delivered normal infants and 28% underwent elective terminations, 3 following the identification of abnormalities. There were a total of 12 infants in whom abnormalities were identified, 3 of which had strikingly similar complex malformations that are clearly a cause for concern. It appears that although most pregnancies exposed to imatinib are likely to have a successful outcome, there remains a risk that exposure may result in serious fetal malformations. (Blood. 2008;111:5505-5508)

Introduction

Imatinib mesylate, the first example of a molecularly targeted therapy, has completely revolutionized the treatment of chronic myeloid leukemia (CML), transforming a fatal disease with a median life expectancy of 6 to 7 years into a truly chronic condition for most patients. The efficacy of the drug coupled with its ease of administration and a low level of toxicity has resulted in many patients leading relatively normal lives. It has been estimated that imatinib could prolong the chronic phase of CML to an average of 12 to 15 years.[1] This in turn has ramifications for the management of the current cohort of patients with CML, and issues relating to quality of life therefore assume far greater importance. These include the ability to parent children.

Imatinib was first administered to patients with CML in June 1998, and it is estimated that there have now been 250 000 patient-years of exposure to the drug (mostly in patients with CML). Despite this experience there is still only limited information on the effects of imatinib on fertility and/or pregnancy. The manufacturer of imatinib recommends that women of childbearing potential should avoid pregnancy while taking the drug. This recommendation is based on the results of animal studies, which showed imatinib to be teratogenic in rats, in addition to general safety concerns surrounding the use of any new drug in pregnancy, and particularly one that targets to eliminate rapidly dividing cells.

The limited data available in the public domain on the outcome of pregnancies of patients exposed to imatinib consist mostly of case studies. Ault and colleagues were the first to publish on a series of 19 pregnancies in which either the male or female partner was undergoing treatment. Although 3 pregnancies ended with spontaneous abortions and 1 with an elective termination, 16 pregnancies were identified to be uneventful.[2] We now report data on a series of 180 women who were exposed to imatinib during pregnancy.

Methods

We investigated the treatment, pregnancy, and fetal outcomes of 180 women exposed to imatinib during pregnancy. Data were initially acquired from physicians who had reported to Novartis, the Hammersmith Hospital in London, or the M. D. Anderson Cancer Center in Houston. Many of these reports had been submitted retrospectively, often a number of years previously, and contained only the information disclosed at the time by the physician. Most of the information submitted to Novartis came from spontaneous reports. Of the 180 cases described, only 28 (15.6%) patients were enrolled in clinical trials. Of these, 16 were from 4 separate trials initiated and led directly by Novartis, and the remaining 12 patients originated from "third-party studies." The collection of pregnancy-related data was not the primary objective of any of these studies. In those studies directly sponsored and coordinated by Novartis, we identified 946 women of childbearing age (defined for the purpose of this analysis as those aged between 17 and 50 years at the time of enrollment) who had been exposed to imatinib, giving an overall pregnancy rate of 16 of 946, or 1.69%. Of the 4 trials, the International Randomized Study of interferon-α (IFN-α) and Ara-C versus Imatinib (IRIS) study involving newly diagnosed patients with CML in chronic phase had the highest incidence of pregnancy, with 7 (4.43%) of 158 women of childbearing age becoming pregnant. Due to a lack of data from comparable studies we are unable to comment on whether this incidence is more or less than would be expected in such a trial. Having reviewed the initial reports, we attempted to contact the relevant physicians by e-mail, letter, and phone, seeking additional information. We sought details of the clinical indication, dose, timing of exposure to imatinib in relation to pregnancy, continuation or cessation of therapy, other medication, maternal age, and outcome of the pregnancy with respect to both maternal and fetal issues. Unfortunately, we were unable to obtain contact details for those physicians who had reported directly to Novartis, as the release of such information to a third party is prohibited by the Data Protection Act. Although efforts were made within the company to obtain the missing data much of the information pertaining to these cases remains incomplete. At the time of writing we still lack pregnancy outcome data for 55 of the 180 cases reported; the missing data are indicated in the results

Submitted October 1, 2007; accepted February 8, 2008. Prepublished online as *Blood* First Edition paper, March 5, 2008; DOI 10.1182/blood-2007-10-114900.

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Table 1. Imatinib pregnancies

Pregnancy outcome	Timing of exposure in pregnancy by trimester, no. of patients					
	Before LMP	First trimester	After first trimester	Throughout pregnancy	Unknown	Subtotal
Spontaneous abortion	0	8	0	7	3	18
Elective termination						
Fetal defects	0	1	0	1*	1	3
Normal or unknown	0	20	0	5	7	32
Stillbirth with fetal defects	0	1	0	0	0	1
Live birth with congenital anomaly	0	6	0	0	2	8
Live birth without congenital anomaly	0	40†	1	18	4	63
Outcome unknown	1	27	3	7	17	55
Total	1	103	4	38	34	180

The table shows the outcome data for 180 pregnancies occurring in women receiving imatinib. It includes 4 women treated with imatinib for gastrointestinal stromal tumors (GISTs), 28 treated for unknown indications, and 5 treated for miscellaneous conditions. The data were collected by Novartis Pharmaceuticals (Basel, Switzerland).

LMP indicates last menstrual period.

*Mother had concomitantly been receiving warfarin therapy. The results of a subsequent postmortem revealed defects typical of warfarin embryopathy.

†Includes 4 patients with exposure in both first and second trimesters.

(Table 1 and accompanying text). Of note, our data include the 10 cases recently reported by the M. D. Anderson Cancer center.[2] Information on the expected background incidence of spontaneous abortions and congenital abnormalities was obtained from published reports.[3-5]

Results

Of the 180 women included in this study, most were being treated for CML (Table 1). The timing of exposure to imatinib by trimester was available for 146 (81%) patients. Of these, 103 (71%) were exposed in the first trimester (including 4 exposed in both the first and second trimesters). A total of 38 (26%) patients received the drug throughout their pregnancy (ie, the drug was not discontinued); this figure includes women exposed up until the time of termination of pregnancy or spontaneous abortion (see Table 1 for outcome details). An additional 4 patients were exposed only after the first trimester.

Pregnancy outcome

Outcome data are known for 125 (69%) of 180 pregnancies. A total of 63 pregnancies resulted in the birth of normal live infants equating to 50% of those with known outcome (KO) or 35% of all pregnancies. 35 women (28% with KO or 19.5% of total) underwent elective terminations, 3 following the identification of fetal abnormalities (Table 2; infants 1-3). The remaining fetuses were either of unknown status or had no defects identified. A total of 18 pregnancies (14.4% KO) ended in spontaneous abortion. Of the remaining 9 infants, there were 8 live births and 1 stillbirth, all with congenital abnormalities (Table 2, "Pregnancy outcome").

Table 2. Summary of congenital defects identified following maternal exposure to imatinib (n = 12)

Fetus no.	Trimester exposure	Pregnancy outcome	Maternal age, y	Imatinib dose (OD), mg	Other medication	Fetal abnormality
1	First	Elective termination	29	300	None	Abnormal ultrasound, elevated AFP
2	All	Elective termination	35	NK	Warfarin, paracetamol, levofloxacin, lorazepam, heparin, prochlorperazine	Warfarin embryopathy: depressed nasal bridge, choanal stenosis, Dandy Walker cyst, ventricular septal defect, coarctation of the aorta, gastroschisis
3	Unknown	Elective termination	37	400	Omeprazole	Cleft palate, polydactyly
4	First	Stillbirth at 34 wk	25	400	Hydroxyurea after first trimester	Meningocoele
5	First	Live birth	35	400	Hydroxyurea	Premature closure of skull sutures
6	First	Live birth	Unknown	NK	None	Scoliosis, small exomphalos
7	First	Live birth, premature at week 30: baby died after 45 min	25	400	NK	Communicating hydrocephalus, cerebellar hypoplasia, atrial septal defect, overriding aorta, ascites, pericardial effusion
8	First	Live birth	27	300	Anagrelide and hydroxyurea (timing unknown)	Hypospadias
9	First	Live birth	29	300	None	Hypospadias
10	First	Live birth	35	400	Hydroxyurea after first trimester	Pyloric stenosis
11	First	Live birth	Unknown	400	None	Hypoplastic lungs, exomphalos, left duplex kidney, right absent kidney, hemivertebrae, and right shoulder anomaly
12	Unknown	Live birth (premature)	Unknown	400	Interferon	Exomphalos, right renal agenesis and hemivertebrae

OD indicates once daily; AFP, alpha fetoprotein; and NK, not known.

Fetal outcome

In total, 12 pregnancies are known to have resulted in infants with fetal abnormalities (9.6% KO); of these there were 8 live births, 1 stillbirth, and 3 terminations (mentioned in "Methods"). The dose (but not the exact duration) of imatinib taken by the mother is known for 10 of these patients. Unfortunately, the data are insufficient to assess any potential relationship between cumulative dosage and the occurrence of fetal abnormalities. Of the infants born with congenital abnormalities, one had premature closure of the skull sutures (craniosynostosis; imatinib stopped within the first few weeks of pregnancy, and subsequent hydroxyurea until term); the second had hypoplastic lungs, exomphalos, duplex left kidney, absent right kidney, hemivertebrae, and a right shoulder anomaly; the third infant had exomphalos, right renal agenesis, and hemivertebrae (imatinib for 3 weeks and interferon at an unspecified time during pregnancy); and the fourth child had a small exomphalos and scoliosis. These last 3 cases are of note, as the combinations of defects were strikingly similar. A further child was born with complex abnormalities, including communicating hydrocephalus, cerebellar hypoplasia, and cardiac defects—this infant was born alive, but died subsequently. A baby with a meningocoele was stillborn. The remaining 3 infants had relatively minor defects only (2 with hypospadias and 1 diagnosed with pyloric stenosis; Table 2). There were no reports of maternal exposure to alcohol, tobacco, or drug addiction during pregnancy in any of these cases. All concomitant medications are detailed in Table 2, and none of the mothers had received any high-dose chemotherapy prior to their pregnancies.

Preclinical studies of fetal organogenesis in pregnant rats showed that imatinib is teratogenic, causing defects such as exencephaly, encephaloceles, and deformities of the skull bones. Female rats given doses greater than 45 mg/kg (approximately equivalent to a human dose of 400 mg/day based on body surface area) experienced significant postimplantation loss with increased fetal resorption, stillbirths, nonviable pups, and early pup mortality. Doses higher than 100 mg/kg resulted in total fetal loss (Novartis investigator's brochure and Novartis clinical safety statement). Imatinib does not, however, appear to be mutagenic or clastogenic (ie, it does not damage chromosomes). Accordingly, patients enrolled in clinical trials of the drug were advised not to conceive while undergoing treatment with imatinib, but inevitably some pregnancies did occur. Although in most patients we have no information regarding the timing of pregnancy in relation to the start date or dose of imatinib, it is likely that most women became pregnant while already receiving the drug rather than starting imatinib only after conception.

Our data show that a significant proportion (50% KO, 35% total) of pregnancies exposed to imatinib result in a normal outcome and a healthy infant. Although our results show a spontaneous abortion rate of 14.4%, which is within the expected limits for the general population (spontaneous abortion rates of 10%-15%[3]), these data may be skewed by reporting bias and the absent outcome data for 55 patients. Of the 51 patients whose pregnancies were reported after a KO (as opposed to at the time of confirmation of pregnancy), 11 (22%) ended in spontaneous abortion, which may suggest an abortifacient effect. Perhaps of more concern are the 12 infants in whom congenital abnormalities were identified. Those with bony abnormalities are especially pertinent, as similar bony defects including exencephaly, encephaloceles, and deformities of the skull bones were observed in the rodent studies. The expected incidence of exomphalos in the general population is approximately 1 in 3000 to 4000 births,[4] and the finding of 3 infants out of 180 is far higher than would be predicted. It is of note that the infants with exomphalos all had a combination of very similar, quite complex defects which would be unlikely to occur by chance and make an imatinib-induced effect more probable.

Russell et al have recently reported that imatinib crosses the mature placenta inefficiently, which might suggest that imatinib is unlikely to play a significant role in the development of fetal abnormalities.[6] However, the mechanism of nutrient supply to the fetus varies at different stages in gestation. Prior to 10 weeks, there are no maternal arterial connections with the intervillous space, and during the first few weeks of development it is thought most likely that the embryo obtains nutrients by simple diffusion from blood pooled in the trophoblastic lacunae. The uteroplacental and fetoplacental circulations and active transport mechanisms are established after the tenth week of gestation.[7] These differences may account for varying effects according to the time of exposure to any individual drug.

However, no information was provided about the ability of imatinib to cross the placenta during the first trimester, the period of greatest risk for fetal malformations.

A total of 10 of the 12 infants with abnormalities are known to have been exposed to imatinib during the first trimester (information unavailable for the remaining 2 infants). Because the mechanism of action of imatinib involves inhibition of tyrosine kinases, it is possible that the congenital abnormalities result from inhibition of members of this extensive family. To date, 90 human tyrosine kinases have been described,[8] of which 58 are receptors. Embryonic development is under complex control, and both c-KIT (a known target of imatinib) and members of the growth factor receptor families (eg, EGFR) may play a role in placental development and angiogenesis. The craniosynostosis syndromes (eg, Crouzon and Apert) are associated with mutations of members of the fibroblast growth factor receptor family;[9] however, this is unlikely to be the underlying mechanism behind the defects seen, as preclinical studies have demonstrated that imatinib has a very low affinity for these receptors (FGFR-1, $IC_{50} = 31.2$ μM as compared with $IC_{50} = 0.025$ μM for Bcr-Abl). A more likely candidate gene is the tyrosine kinase receptor PDGFRα (platelet-derived growth factor receptor α)—a known target of imatinib to which the drug binds with high affinity ($IC_{50} = 0.1$). Mice homozygous for null mutations in PDGFRα show combinations of birth defects, including facial clefting, severe spina bifida occulta, cardiac defects, omphalocele, renal and urogenital anomalies, and vertebral and rib fusion abnormalities.[10,11] PDGFRα also appears to play a role in lung development, as shown in studies with PDGFRα-null mice that also carried a human YAC PDGFRα transgene, with pups dying soon after birth due to lung hypoplasia.[12]

Discussion

The data in our retrospective study are mainly derived from spontaneous reports, and the study is obviously affected by the lack of complete information for all pregnancies despite strenuous efforts to obtain this. The high rate of termination is understandable, as it is likely that many of the pregnancies were unplanned. Despite these limitations, we consider our findings to be representative of the expected outcome and feel that this report still represents the most comprehensive set of data on the effect of imatinib on pregnancy and is therefore very relevant to patients and physicians.

Our data indicate that concern is justified, and that all female patients should be advised to avoid conception while taking imatinib. In the patient who does become pregnant while on treatment, balancing the risk to the fetus of continuing imatinib versus the risk to the mother of interrupting treatment remains difficult. From the fetal perspective, imatinib should be discontinued due to the potential risk of serious developmental abnormalities; from the maternal perspective, however, this may not be appropriate. Another option would be to continue imatinib and have the pregnancy closely monitored, considering termination should any significant abnormalities be identified. In these circumstances, the couple should be made aware of potential risks, particularly of first-trimester exposure. Considerations include the wishes of the parents, the mother's disease status, the availability of suitable alternative therapies, and the ability to reinduce responses to imatinib after a prolonged period off treatment.

We have previously reported[2] 10 women (9 in complete hematologic response [CHR]) who interrupted treatment with imatinib due to pregnancy. Of the 9 patients in CHR when the imatinib was stopped, 1 was in complete cytogenetic response (CCyR), 3 were in partial cytogenetic response (1%-34% Ph^+ metaphases), and 2 were in minor cytogenetic response prior to interruption of therapy. A total of 6 of the 9 patients had an increase in Ph^+ metaphases, and 5 lost their CHR while off treatment. At a median of 18 months since restarting imatinib, these 9 women were again in CHR, and although all had a cytogenetic response, this was complete in only 3 patients. This might be considered a poor response, as the rate of CCyR at 18 months in patients who received uninterrupted imatinib from diagnosis is 75% to 90%. However, as a group, these 9 women showed improved responses to treatment following pregnancy when compared with their results before pregnancy. Reassurance that imatinib can be discontinued in some patients under certain favorable circumstances is provided by a recent report by Rousselot et al.[13] Imatinib was discontinued in 12 patients who had all been in complete molecular remission for a period of at least 2 years. Of these 12, 6 (50%) patients developed molecular relapse within 5 months of stopping imatinib therapy, but the remaining 6 continued to have undetectable BCR-ABL transcripts at a median of 18 months' follow-up. Of those who relapsed, most again achieved a complete molecular response within a relatively short period following reintroduction of imatinib.

In conclusion, exposure to imatinib during pregnancy might result in an increased risk of serious fetal abnormalities or spontaneous abortion. Women of childbearing potential should use adequate contraception while taking imatinib. Imatinib should be avoided in pregnancy unless the risk of interrupting therapy is deemed by the patient's physician to be unacceptable. In cases of accidental or planned pregnancy, risk/benefit evaluations must be carried out on an individual basis with careful counseling of both parents using the most recent data available. Alternative therapies for CML include IFN-α. Animal studies have shown this drug to be nonteratogenic in rats and rabbits, resulting in normal offspring, but it has also been shown to have abortifacient effects in rhesus monkeys at doses of 90 and 180 times the recommended intramuscular or subcutaneous dose of 2×10^6 IU/m^2. In view of this, the official recommendation is that IFN-α be avoided during pregnancy unless "the potential benefit justifies the potential risk to the fetus" (IntronA study of product characteristics). The treatment of CML during pregnancy remains a considerable clinical challenge. The intended establishment by Novartis of an international pregnancy registry may provide further information as experience with imatinib continues to increase.

Acknowledgments

J.F.A. is grateful for support from the National Institute for Health Research Biomedical Research Centre Funding Scheme (United Kingdom).

Authorship

Contribution: S.M.P. wrote the manuscript and analyzed/interpreted data; J.C., A.H., H.K., and G.R. contributed data and reviewed the manuscript; P.A. and R.P. collected and analyzed data; and J.F.A. was responsible for the conception and integrity of the manuscript.

Conflict-of-interest disclosure: A.H. and R.P. are both employees of Novartis, the company that manufactures imatinib. J.F.A. is a member of a national clinical advisory group and has received honoraria for independent presentations at regional and national company-sponsored meetings. J.C. has received research funding from Novartis. G.R. has received honoraria from Novartis. S.M.P. has no conflicts of interest to declare. This work did not receive any external funding.

Correspondence: Seonaid M. Pye, Clinical Research Fellow, Division of Investigative Science, University College London, Hammersmith Campus, Du Cane Road, London, United Kingdom W12 0NN; e-mail: s.pye@imperial.ac.uk.

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