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Outcome of pregnancy in chronic myeloid leukaemia patients treated with tyrosine kinase inhibitors: Short report from a single centre

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ABSTRACT

Background: The aim of this work was to report on the outcome of pregnancy in patients with chronic myeloid leukaemia who were on tyrosine kinase inhibitor treatment.
Patients and methods: We report the result of 22 pregnancies in 14 patients (9 female and 5 male) who conceived or their partner conceived while being on tyrosine kinase inhibitors for their CML.
Results: All pregnancies except one were uneventful. 25 newborns were born and except in one case where small atrial septal defect was diagnosed, all infants were healthy and showed normal development after birth.
Conclusion: This small series does indicate that parents can most likely expect an uneventful outcome to a pregnancy despite exposure of either partner to TKIs. There is no consensus or guideline regarding the best practice in case of pregnancy. More reports of similar nature would certainly be beneficial to practitioners and patients alike. As such it is still recommended to practice effective contraception during the period of TKI treatment.

1. Introduction

Chronic myeloid leukaemia (CML) is a clonal myeloproliferative neoplasm of a pluripotent stem cell first described by John Hughes Bennett in 1845 at the Royal Infirmary of Edinburgh [1]. CML was the first malignant disorder in which a specific chromosomal abnormality was identified and this has been known as Philadelphia (Ph) chromosome [2,3], which is the result of a reciprocal translocation between chromosomes 9 and 22. It involves the ABL1 proto-oncogene in chromosome 9 and the BCR gene in chromosome 22 [4,5]. This fusion results in dysregulation of intracellular signalling that drive cells to increased proliferative activity and resistance to apoptosis [6]. Imatinib mesylate is an orally bioavailable 2-phenylaminopyrimidine with targeted inhibitory activity against the constitutively active tyrosine kinase of the BCR-ABL chimeric fusion protein [7]. Imatinib was the first approved molecular targeted therapy in the field of haematology & oncology. Imatinib mesylate (Gleevec, Novartis Pharmaceuticals Corporation, East Hanover, NJ) has revolutionised the treatment of CML with marked improvement in the survival of patients in all phases of disease. Imatinib produces complete cytogenetic response in about 90% of patients, but there are cases of primary or secondary resistance to imatinib [8,9]. New generation tyrosine kinase inhibitors (TKIs) are more potent and effective than imatinib and they produce more rapid optimal response to treatment. Imatinib mesylate and 2nd generation TKIs have become the standard of care in the management of patients with newly diagnosed CML. The use of TKIs in the treatment of CML has led to a transformation of CML from a fatal disease without intensive intervention to a chronic disease by extending the life expectancy and the long term prognosis of patients with CML and significantly decreasing the risk of disease progression to more advanced phases [10]. Despite the extensive clinical experience with TKIs, the available information about the effects of TKIs on fertility, pregnancy, and the outcome

Abbreviations: CHR, complete haematological remission; CCgR, complete cytogenetic response; MCgR, major cytogenetic response; PCgR, partial cytogenetic response; MMR, major molecular response; CMR, complete molecular response; IFN, interferon; Ph, Philadelphia; CML, chronic myeloid leukaemia; PCR, polymerase chain reaction; Q-PCR, quantitative polymerase chain reaction; TKIs, tyrosine kinase inhibitors; ELN, European Leukaemia Network.

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of babies who were exposed to TKIs for a variable length of time during pregnancy and lactation, is limited [11]. The vast majority of information is derived from animal studies [12–16]. TKIs are usually well tolerated and their uses have resulted in durable high response rate. After almost 14 years of follow-up in patients treated with imatinib in the initial trials, there has not been any evidence of long-term adverse clinical outcome of treatment with imatinib. Although the median age of diagnosis for patients with CML is in sixth decade, about 25% of patients are diagnosed before age of 40. This younger subset of patients with CML is faced with the dilemma of making decisions regarding childbearing and continued control of their disease [11,12,21]. The TKIs have very good safety profile, but animal studies have shown that they are potentially teratogenic [13–16]. As such, currently these drugs are not recommended for use during pregnancy or if the female patient plans to conceive. Since the discovery of imatinib, there have been developments of more effective tyrosine kinase inhibitors, e.g., nilotinib, dasatinib, bosutinib, ponatinib. The manufacturers of TKIs recommend that women of childbearing potential should avoid pregnancy while taking the drugs. In case of planned or incidental pregnancy, other therapeutic options should be recommended.

In this paper, we report the outcome of pregnancies in patients treated with TKIs who became pregnant and who conceived whilst receiving TKI therapy.

2. Patients and methods

From June 2001 to December 2009, 105 patients were diagnosed with chronic phase CML and treated with TKIs. All patients signed a detailed general consent form upon admission to hospital. This consent form was approved by the Regional Ethical Committee, and it contained patients' agreement on; necessary diagnostic work-up including invasive procedures, use of laboratory findings, treatment outcome, and publication of these data.

Prior to the start of treatment, detailed instructions were given to all patients about the administration and possible adverse effects of each type of treatment. Patients on hydroxyurea and TKI treatment were clearly instructed to adhere to strict contraception protocols during the whole period of therapy. Patients were closely observed and monitored on monthly basis until they achieved CHR and thereafter every 3 months. Treatment algorithm and remission assessment were based on the European LeukemiaNet (ELN) guidelines (https://www.leukemia-net.org). Drug toxicity was assessed on each follow-up visit and was graded according to the Common Toxicity Criteria (Common Terminology Criteria for Adverse Events) version 2.0 published by National Cancer Institute (NCI).

3. Results

Nine female patients conceived whilst being on TKI treatment, mainly imatinib mesylate. This resulted in 16 pregnancies and two patients gave birth to three newborns each. The age of patients ranged between 22 and 43 years. All patients had uneventful normal delivery. The duration of exposure to TKI was variable, but in the majority of cases the patient was on TKI therapy from the time of conception, which continued during breast-feeding as well. Six patients were in MMR or better and two were in CCgR when the pregnancy was confirmed. One patient had three uneventful pregnancies whilst being on three different TKI each in different pregnancy. She also had two sessions of leukapheresis in her first pregnancy. This is a unique case of CML in pregnancy that was treated with different types of TKI treatment in each pregnancy.

Four female patients received alpha-interferon and one was treated with pegylated alpha interferon for variable periods during pregnancy and breast-feeding. All patients maintained molecular remission during pregnancy and breast-feeding and all had uneventful deliveries. Only one newborn girl was diagnosed of small primum atrial septal defect at age of 30 months. In this case, the mother was on imatinib treatment after the 8th week of gestation when the development of heart has already been completed. The minor cardiac malformation was successfully repaired surgically. There was no abnormality in the remaining 15 newborns. All 15 newborns had normal growth and development, despite exposure to TKI therapy during pregnancy and/or breast-feeding (Fig. 1).

We also report on five male patients who were in MMR when their female partners became pregnant. The resultant conceptions led to 6 male and 4 female healthy newborns. In two cases, the patient's partner conceived twice and in one of these 2 cases, the male patient was on nilotinib therapy. There was one case of twins and another case of triplets. All these pregnancies were uneventful and all 10 newborns were healthy.

4. Discussion

The management of CML during pregnancy poses a therapeutic dilemma because of the potential teratogenic effect of therapy. The incidence of CML associated with pregnancy is estimated to be 1 in 100,000 [11]. The introduction of the TKIs in clinical practice has markedly changed the prognosis of CML patients. Treatment with TKIs provides an effective disease control with relatively few adverse reactions, near normal lifestyle and extended life expectancy for the majority of patients. A considerable number of young patients with CML are in reproductive age and this group of patients is faced with making a difficult decision regarding conception or continued control of their disease. This fact has brought the necessity to address issues relating to fertility and pregnancy. The proper management of CML in pregnant patients presents a challenge to the treating physician and it requires delicate attention to important issues including medical, ethical, psychosocial and cultural sensibilities. In countries where termination of pregnancy is unacceptable because of any reason, the management of pregnant lady with CML is even more challenging. In pregnancy, two lives are at stake. The patient, who deserves the best of the therapeutic options available and the foetus that may be affected by the teratogenic effects of treatment offered to the mother [11–16]. Currently the recommended 1st line treatment of CML is TKI, but this option is not recommended for patients who are pregnant or planning to conceive. Alternative therapeutic options for CML in pregnancy are; leukapheresis [17], alpha-interferon [18], and hydroxycarbamide [19]. The safety and feasibility of leukapheresis and interferon have been published in previous reports. Hydroxycarbamide inhibits RNA synthesis and is known to cause embryotoxicity in animal species, however, the exact effect of hydroxycarbamide on developing human foetus is not well-established [19]. Available data on the outcome of pregnancy in patients exposed to imatinib and other TKIs are still limited [20]. They are mainly based on information derived from animal studies. In pre-clinical studies imatinib mesylate was found to be teratogenic (not gonadotoxic) in mice and rats but not in rabbits. Female rats receiving doses greater than 45 mg/kg which is approximately equivalent to human dose of 400 mg/day based on body surface area, delivered youngs with different types of defects such as exencephaly, encephaloceles, and deformities of the skull. Doses higher than 100 mg/kg resulted in complete foetal loss [21,22]. Regarding nilotinib, genotoxicity studies in mammalian systems did not show evidence for mutagenic potential, but it resulted in embryotoxic and fetotoxic effects in rats and rabbits at dosage which produce maternal toxicity [21]. Both imatinib and nilotinib and their metabolites were secreted into milk, but they do not cross placenta [21]. In case of dasatinib, even the lowest dose resulted in embryo-foetal toxicities and also secreted into milk [21]. It is routine practice to exclude gravid and lactating patients from studies in which new drugs are investigated, particularly antineoplastic medicines. Thus it is almost impossible to assess the safety of these new agents during pregnancy and, therefore reports of similar instances as described above remain the sole informative source on their clinical behaviour. As