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About a Case of Chronic Myeloid Leukemia and Pregnancy

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Abstract

Chronic myeloid leukemia (CML) associated with pregnancy is a very rare situation (less than one case per 100,000 pregnancies). It raises a serious ethical and therapeutic problem because chemotherapy during pregnancy can expose the fetus to various complications such as congenital malformations, abortion and intra uterine growth restriction. Inhibitors of tyrosine kinase are the most widely used molecules but without much certainly about their non-teratogenic effects. This is a report case of pregnancy occurring in a patient with Imatinib for CML replaced by Hydrea who gave birth to a healthy newborn with no congenital malformation.

Keywords

Chronic Myeloid Leukemia, Pregnancy, Tyrosine Kinase Inhibitors

1. Introduction

Chronic myeloid leukemia (CML) is a slowly progressive (chronic) form of leukemia affecting the myeloid white blood cells in the bone marrow and has several names, including:

- Chronic myeloid leukemia
- Chronic granulocytic leukemia
- Chronic myelocytic leukemia

The World Health Organization (WHO) classifies CML as a myeloproliferative syndrome. In this type of disease, the bone marrow produces an excess of red blood cells, white blood cells or platelets. Patients with it usually worsen slowly as excess cells build up in the blood or bone marrow. Anemia, fatigue, repeated infections and bleeding can result.

It is a rather rare disease. In 2016, its incidence was 1.8 per 100,000 inhabitants. CML affects men a little more than women and especially adults. The median age of patients at diagnosis was 64 years. Very few children are affected by CML [1].

Fortunately, the association of pregnancy and leukemia is rare, one in 100,000, and for CML associated with pregnancy, it is 10% of cases [2] [3].

The rarity of this association is due to:

- the average age of onset of most leukemia, much higher than the average age of onset of pregnancies.
- the very rarity of leukemia, the overall incidence of which is far lower than that of breast cancer, for example. This scarcity explains the absence of large prospective studies.
- concerning the diagnosis and therapeutic management of the patient, but also the follow-up of the child's future [4] [5].

In general, treatment of a pregnant woman with leukemia can be associated with high fetal morbidity, related to both the treatment and the underlying pathology, up to fetal death or severe malformations. Regarding the management of CML during pregnancy, current treatments are, in theory, contraindicated. These include, among others, tyrosine kinase inhibitors (TKIs). In the case of a concomitant diagnosis of pregnancy and CML, the first line attitude is to initiate treatment with alpha interferon, because it is not teratogenic on the one hand and on the other hand, the chances disease progression over a relatively short period of less than a year are low. If the patient cannot tolerate alpha interferon, first generation TKIs can be used, in this case Imatinib, even if pregnancy is considered a contraindication to its use. pregnancy in a patient known to have CML and treated with TKIs, it is recommended to observe two years of complete molecular remission before considering discontinuation of treatment with TKI and planning a pregnancy [5].

2. Case Presentation

This is a 25-year-old woman referred from a private center to the CUK for better management of a 100,000/mm^3 hyperleukocytosis discovered by chance after an assessment of the development of a pain syndrome of the iliac fossa right (FID). His antecedents were marked by:

- A notion of hypertension and diabetes in his 2 parents.
- She is 2nd in a family of 7 children including 3 girls and 4 boys and all her siblings are alive and in apparent good health.
- She lives in a common-law relationship and her partner who is a civil servant is in apparent good health.
- She is a housewife, and does not suffer from diabetes mellitus or high blood pressure.
- She does not consume alcohol or tobacco.

Regarding her obstetric history, she was a 25-year-old primipara primigeste

and she saw her menarche at the age of 12, she has an irregular menstrual cycle, the duration of her periods is 5 days, they are eumenorheic with a normal flow. She has never had an abortion.

Her physical examination was trivial and at the end of it a myelogram was requested, the result of which revealed a strong hyperplasia of the neutrophil granulocytic line with differentiation giving a chronic myeloproliferative syndrome corresponding to chronic myeloid leukemia (CML) which will be confirmed by the search for the Philadelphia Chromosome detected at the 70% level confirming the progressive nature of the disease. Other results of assesments were: hemoglobin level at 7.4 g/dl, leucocytis at $1.1 \times 10^3/mm^3$. The patient will be put on Imatinib at a rate of 200 mg/day, which she will take for 18 months from September of 2015. The course of the disease will be characterized by the diagnosis of an early pregnancy. Imatinib will be replaced by hydroxyurea given the high teratogenic risk of this one (Imatinib). The pregnant woman was then referred to the Obstetrics service of the Department of Gynecology and Obstetrics of the University Clinics of Kinshasa for treatment of her pregnancy.

She will start antenatal care (ANC) at the 33rd week of pregnancy according to the date of her last period.

The physical examination was trivial and the assessment requested during this first ANC revealed:

- An hemoglobin level of 10.3 g/dl
- The white blood cell count at $7100/mm^3$
- Sédimentation rate at 78 mm/h
- The blood group = B Rh+

The ultrasound performed on 30/01/2018 showed an evolving pregnancy of 32 weeks with amenorrhea, without any malformations detected.

The course of antenatal care (ANC) will be marked by the occurrence of two episodes of vaginitis at the 33rd and 37th week of amenorrhea with a good course.

On March 9, 2018, she will complain of low back hypogastralgia for which she will consult and after examination, the general condition was good, and it will be noted good constitution, good nutritional status, the palpebral conjunctivae were well colored and the bulbar conjunctivae anicteric, his weight at 70.1 kg and a height at 1.63 m, a blood pressure at 130/70 millimeters of mercury (mmHg). The obstetrical examination noted mainly a uterine height of 31 cm, fetal heart sounds at 144 bpm, slight uterine contractions, on vaginal examination, the cervix was 50% effaced and dilated to 1 cm, with a good pelvis, the cephalic presentation initiated. The examiner has concluded that labor has started and she will be transferred to the delivery room.

When she was admitted to the delivery room, the reassessment made noted the same elements as the first consultation.

The delivery room team concluded that the onset of labor was to exclude a false onset of labor in a 25-year-old P1 G1 with a 39-week, 5-day pregnancy with

chronic myeloid leukemia.

In the program, she had to perform the hemoglobin level, an obstetric ultrasound and a tocography. From the requested assessment, the ultrasound had shown an evolving monofetal pregnancy of 37 weeks, cephalic presentation, amniotic fluid in sufficient quantity and the placenta was normally inserted. Tocography showed an excitable uterus with basal tone of 12 mmHg during the first half and 20 mmHg during the second half with uterine contractions up to 100 mm Hg.

The reassessment made 2 hours later had noted weak uterine contractions, a cervix 75% erased and dilated to 3 cm. Given these elements, the delivery room team concluded that labor was in its latent phase and allowed the process to evolve by suggesting maternal-fetal monitoring under a monitor and in the left lateral decubitus position.

Labor has proceeded normally and she will give birth to a newborn female with an APGAR of 8/9/9, who weighed 2800 g for a size of 48 cm and a PC of 33 cm, without objectified congenital malformation. The pediatrician who examined the newborn concluded that a eutrophic term newborn was okay and left it with its mother.

The postpartum consequences were unremarkable and the mother continued her long-term treatment for CML with hydroxy urea (hydrea®) at a dose of 2 × 500 mg/day orally.

3. Discussion

Very few studies have discussed the interaction of TKIs with pregnancy; however, a study of 13 conceptions [6] noted that 4 of them resulted in normal pregnancies carried to term, 2 resulted in therapeutic termination of pregnancy and 3 in spontaneous abortions. Another study [7] [8] noted in 60 pregnancies, no abnormalities except extra rotation of the stomach and miscarriage. A finding was made, that if Imatinib is started after organogenesis, these pregnancies did not present any problem, on the other hand, if it was given before or during the first trimester of pregnancy at doses of at least 800 mg/kg/day, it was found to be teratogenic with encephalocele-like malformations, exencephaly and malformation of the frontal and parietal bones [8].

Regarding hydroxyurea (hydrea®), animal experiments have observed abnormalities such as heart, skeletal, genitourinary, cerebral and ocular malformations [9]. However, in pregnant women, the data in the literature are not alarming [9]. This is undoubtedly due to the fact that the doses tested in animals are 10 to 100 times higher than those used in human medicine [9].

Regarding children born to mothers who were on Imatinib, the literature tells us that their outcome is rather reassuring, even if their birth weight seems to be reduced and the risk of malformations remains present. Unfortunately, no data on long-term toxicity in children exposed in utero are available and therefore a delayed effect on exposure cannot be excluded [10]. The largest recently pub-

lished series includes 180 pregnancies under Imatinib, 55 of which the outcome is not known. The majority of pregnancies in which women have been exposed to Imatinib resulted in normal childbirth (70% of pregnancies with known outcomes). The spontaneous abortion rate was 14.4%, a rate comparable to that of the general population. However, there is an undeniable risk of malformation and some malformations are reminiscent of those observed in animal experiments [10].

4. Conclusion

The experience of our clinical case where we interrupted, as soon as the onset of pregnancy, the treatment based on Imatinib, to replace it with hydroxyurea (hydrea®), is in agreement with the literature, because the mother and the child evolved very well throughout the pregnancy; the maternal blood count remained normal throughout the pregnancy and at delivery, no malformation was detected in the newborn, who to date is doing well, as is his mother.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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