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Case Report

Outcome of Pregnancy in the Era of PEGylated Interferon-α2a in Females with Chronic Myeloid Leukemia: An Experience from Qatar

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Abstract
Chronic myelogenous leukemia (CML), also known as chronic myeloid leukemia, is a myeloproliferative neoplasm characterized by increased proliferation of the granulocytic cell line without loss of its capacity to differentiate. It accounts for 20% of all adults affected by leukemia. Tyrosine kinase inhibitors revolutionized the treatment for CML and improved quality of life. Fertility is an important issue for both males and females. Here, we report our experience with a pregnant female with CML, and shed light on safety and efficacy of PEGylated interferon-αa in pregnant women with CML and its outcome.

Introduction

Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm characterized by the *BCR-ABL* oncogene, which results from a reciprocal t(9; 22) chromosomal translocation. CML constitutes 15% of adult leukemia. Incidence rates vary from 0.6 to 2.0 cases per 100,000 persons, increase with age and are higher in men than in women. The average age at diagnosis of CML is around 64 years [1]. However, CML can affect any age group. In fact, approximately 17% of cases occur in the age group of 20–44 years. Fertility in CML patients receiving tyrosine

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kinase inhibitors (TKIs) has been addressed in certain studies, which concluded that, in male patients with CML receiving TKIs, there is a notable decrease in sperm parameters and decreased concentrations of serum T, LH, and FSH [2].

On the other hand, despite the advancement in treatment options, we still have limited data on the safety of TKIs in pregnancy and their effect on fertility. There remains a concern for the occurrence of rare congenital malformations and spontaneous abortions in association with TKI therapy, mainly with imatinib [3, 16]. Management in pregnant females with CML remains challenging for both, patient and physician, given the risks on the fetus upon continuing the therapy versus the patient risk of withholding the treatment and potentially losing optimal disease response [3].

Case Presentation

A 43-year-old Filipino female patient, diagnosed with CML (chronic phase) was started on dasatinib as upfront therapy, and achieved complete hematologic, cytogenetic and molecular major response as per the ELN (European leukemia net) recommendations (2013). The patient got pregnant while on dasatinib, which mandated its immediate stoppage.

Alternatives were discussed with the patient: (1) to start with conventional interferon (safe and recommended); (2) to start with PEGylated interferon, but there is no data confirming its safety in pregnancy; (3) to take neither interferon nor TKIs, but this is a risky approach since the patient can progress to either an accelerated phase or blast crisis as a worst case scenario or remain in the chronic phase, which would be the best scenario, but this is not guaranteed. The patient and her husband opted for PEGylated interferon. She was referred to a high-risk pregnancy unit in the maternity hospital for close follow-up. Follow-up throughout pregnancy showed a normal fetus with no evidence of teratogenicity.

Discussion

The current management of pregnant patients with CML is a therapeutic challenge. Patients may initially present with CML while pregnant or may become pregnant while on active treatment.

Patients presenting with CML in the chronic phase must be assessed and are less likely considered for elective termination, even at the beginning of their pregnancy [4].

While in advanced phases (accelerated or blastic phases), the patient must be managed more aggressively and may need immediate intervention with TKIs. However, it is known that TKIs must not be used during pregnancy, especially during the first trimester, to consent the development of the organs.

Current treatment approaches include supportive care with interferon-alpha-2a (IFN-α2a) and leukapheresis [5]. Leukapheresis is not a favored option due to its limited availability, complications and poor tolerance to its frequency [5].

IFN-α is considered safe in pregnancy [6]. It acts by controlling CML by directly inhibiting cell proliferation of the Ph+ clone (protein synthesis, RNA breakdown), inducing an immune modulation, or eliciting a bone marrow microenvironment regulation of hematopoiesis [7].

It has been extensively studied as treatment for patients with CML resulting in hematologic remissions in the majority of patients treated with single-agent IFN-α [8–11].

On the other hand, interferon is known to cause significant side effects, such as fever, chills, and flu-like symptoms; in addition, it has a short half-life as it is barely detectable in the

serum 24 h after its administration, requiring multiple frequent administration (2 or 3 times weekly) for sustained efficacy [12]. This makes it a less favorable option.

However, to overcome this limitation, 2 forms of PEGylated (covalent attachment of polyethylene glycol [Peg]) IFN-α have been developed: Peg-IFN-α2a and Peg-IFN-α2b. The PEGylating resulted in different properties and pharmacokinetics, including sustained absorption/exposure and the prolonged half-life reduced clearance compared with IFN-α2a, allowing for once weekly doses [12, 13], attributing to better compliance with the medication.

Our patient had good compliance. She was followed up throughout her pregnancy at the high-risk pregnancy unit in the maternity hospital, and the outcome was a normal fetus with no teratogenicity.

Conclusion

PEG-INF might be the option for treatment of CML during pregnancy. So far, efficacy and safety of PEG-IFN in CML treatment have been investigated in several trials in combination with TKIs [14, 15], but it has not yet been investigated in pregnant women with CML.

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Statement of Ethics

Written informed consent was obtained from our patient to allow the publication of information.

Disclosure Statement

The authors have nothing to disclose.

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Authors Contributions

Mohammad Abu-Tineh: writing the manuscript. Nancy Kassem, Mohammad Abdul-Jaber Abdulla, Omar Mohammad Ismail, Khaldun Obeidat, and Rola Ghasoub: clinical care. Mohamed A Yassin: writing and editing.

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