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Case Report

Teratogenic effect of decitabine in a pregnant patient with acute myeloid leukemia: a case report

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Introduction

Hypomethylating agent (HMA) such as azacitidine and decitabine are currently approved for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia especially in those patients who are ineligible for more intensive treatments. However there is scarce information on the side effects of HMA on fertility and/or pregnancy. The manufacturer of HMA recommends that women of childbearing potential and men with female partners of childbearing potential should use effective contraception and avoid pregnancy while taking HMA, which is based on the preclinical studies in mice and rats which showed HMA was teratogenic, fetotoxic, and embryotoxic.[1] The administration of chemotherapy during the first trimester of pregnancy is often a concern due to the potential risk of teratogenicity. The purpose of this paper is to describe a case of refractory acute myeloid leukemia (AML) who got pregnant during decitabine chemotherapy, and to discuss on the underlying possibilities of the fetal anomalies observed.

Case report

This is a 39-year-old Iban lady who was diagnosed with AML in October 2015. A general practitioner first referred her to us for 1-week history of fever and abnormal blood counts. Besides the fever she had no other constitutional symptom or significant bleeding tendency except spontaneous bruising over limbs prior to the onset of fever. She is a housewife and is married with 4 children aged between 2 to 16 years of age. She has underlying chronic hepatitis B infection for which she is not on treatment. On examination, she was pale but not jaundiced. There was no lymphadenopathy or hepatosplenomegaly. Her initial presenting counts were hemoglobin (Hb) of 9.3 g/dL, white blood cell (WBC) of 68×10^9/L and platelet of 17×10^9/L. Her bone marrow aspiration and trephine (BMAT) were consistent with AML with normal cytogenetic karyotype. However molecular genetic analyses detected the FLT3-ITD mutation.

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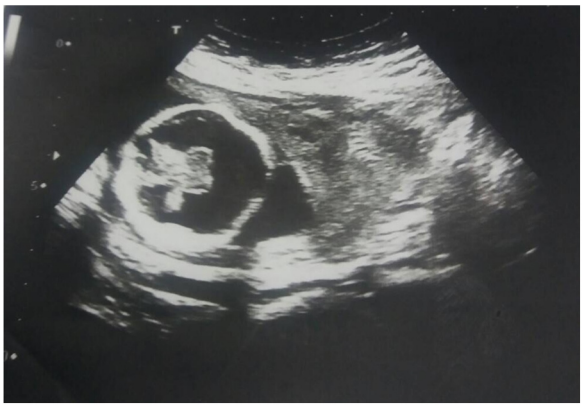


Figure 1 – Evidence of holoprosencephaly from scan.

After counseling, she was agreeable for treatment and underwent standard induction chemotherapy daunorubicin and cytarabine (DA 3+7) and started tenofovir for her underlying chronic hepatitis B. However her repeat BMAT post-induction was in keeping with refractory disease. She was then given a salvage regime of fludarabine, cytarabine and idarubicin (FLAG-Ida). Her repeat BMAT assessment after FLAG-Ida was in remission morphologically but flow cytometry showed presence of 1.8% cluster of blasts, in keeping with residual disease. Patient was then given another cycle of salvage chemotherapy FLAG seven weeks later after full recovery. At the same time she was worked up for allogeneic stem cell transplantation. However, there was no matched donor found from her two siblings as well as from local matched-unrelated donor (MUD) registry. Her repeat BMAT post-FLAG was in remission. In view that patient had no option for allogeneic stem cell transplantation, she was counseled for maintenance therapy with six cycles of decitabine in which she agreed. The first cycle of intravenous decitabine, in the dose of 10 mg/m^2 for 5 days every 28-days, was given on 15th July 2016. She did not experience severe episode of neutropenic sepsis during her courses of decitabine. Her last 6th cycle was given on 7th February 2017. Unfortunately she defaulted follow-up since discharge on 11th February 2017.

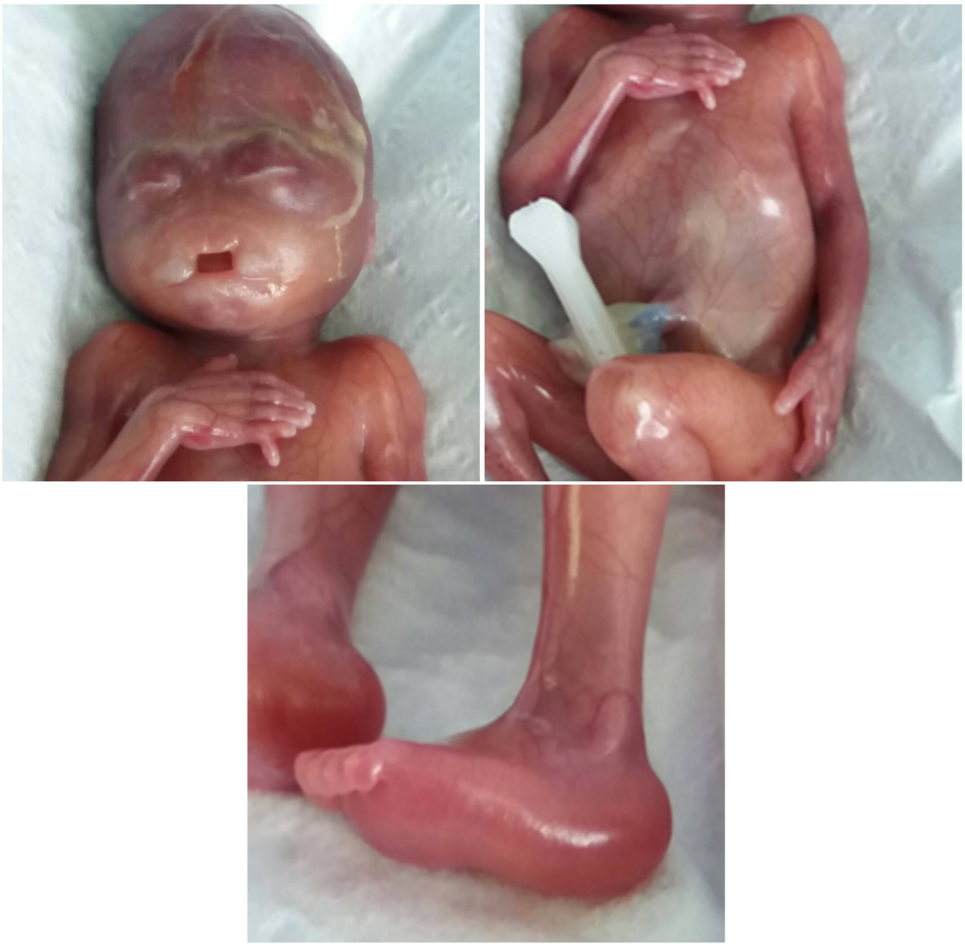
She presented again to obstetric clinic in Ampang Hospital on 5th June 2017 for booking as she was found to be pregnant with her 5th pregnancy. However she was not sure of her date. Her first antenatal ultrasound scan then showed a single fetus with parameters measurement corresponding to 16th week of gestation. She was planned for a detail scan at 18th week at combined clinic with haematology team. Unfortunately, the detailed scan done on 20th June 2017 showed that the fetus has developed multiple congenital anomalies such as holoprosencephaly, absence of nasal bone and cleft lip and palate (Fig. 1). Parameters measurement was in keeping with gestational age of 17th to 18th week. Liquor was adequate with fetal heartbeat seen. Her blood investigations including a full blood count and random blood sugar were normal. She denied intake of any medication or traditional supplements since her last dose of chemotherapy. As the extent of anomalies was not compatible with life, patient and husband were counseled for termination of pregnancy (TOP). The TOP was performed on 27th June 2017. Fetus passed out after 2 cycles of cervagem. The fetus had normal cord but there was evidence of multiple congenital anomalies including hypotelorism, mid-facial deformity, absence of nasal bone, cleft lip and palate, polydactily and rocker-bottom feet (Figs. 2–4). Patient was discharged well the next day with a plan for bilateral tubal ligation procedure at a later date. She was last seen in clinic on 3rd January 2018 with Hb level of 13.0 g/dL, WBC of 6.95 $\times$ 10^9/L and platelet of 284 $\times$ 10^9/L. She was keeping well.

Discussion

Epigenetic changes, such as aberrant DNA methylation, have an important place in the pathogenesis of MDS and AML.[2] Hypermethylation-induced gene silencing of tumor suppressor and other cancer-related genes plays a fundamental role in human tumorigenesis.[2] In contrast to structural changes such as mutation or deletion causing permanent loss of gene expression, epigenetic changes can be pharmacologically reversed, resulting in gene re-expression and restoration of normal cellular functions.[3] The rationale behind demethylation therapies is the ability of DNA methyltransferase inhibitors to revert hypermethylation-induced gene silencing. Azacitidine and decitabine are two HMAs approved for the treatment of various hematological conditions. Originally, they were intended as cytotoxic drugs. However, it was discovered that a low dose of these drugs could cause DNA demethylation by inactivation of DNA methyltransferase-1 (DNMT-1), the enzyme responsible for methylation of the DNA.[2] Hence low dose of HMA is able to induce re-expression of previously silenced genes. Reactivation of cell cycle-regulating genes that were initially silenced due to hypermethylation may induce cell differentiation, reduce proliferation and/or increase apoptosis of the tumor cells.[4] The common side-effects of HMA includes fatigue, nausea and myelosuppression but at its therapeutic dose, they are generally well tolerated with manageable side-effects.

There is no adequate data on the use of azacitidine or decitabine in pregnant women and in fetal outcome. Studies in mice have shown reproductive toxicity.[1] Azacitidine in mice and rats produced a dose-dependent decrease in offspring survival, fetal weight with an increase incidence of microphthalmia and exencephaly.[5] 5-azacytidine is also found to be associated with neuronal cell apoptosis in mice during the late weeks of pregnancy.[6] Hence all men and women of childbearing potential should be advised to practice effective contraception to avoid pregnancy while on HMA and up to at least 3 months after completion of therapy.

Holoprosencephaly in an abnormality of brain development in which the brain does not properly divide into the right and left hemispheres.[7] This condition can also affect development of the head and face. Holoprosencephaly can be caused by mutations of genes, chromosome abnormalities presenting as a feature of several genetic syndromes and by environmental factors such as teratogens, gestational diabetes or transplacental infections. In many cases however, the exact cause remains unclear. In this case, it was believed that the patient may have conceived soon after her last 6th cycle of decitabine. Her last dose of decitabine was approximately 4 month ago and the ultrasound assessment on presentation



Figures 2–4 – Fetus with normal single cord but complicated with hypotelorism, mid-facial deformity, absence of nasal bone, cleft lip and palate, polydactily and rocker-bottom feet.

was corresponding to 16th week of gestation. At that time she has had no gestational diabetes and she denied any new medication ingestion since her last therapy in February. In this case, however, there was no further cytogenetic or molecular testing done to investigate for the possibility of genetic causes.

Conclusion

The malformations found in this fetus highlight the possibility of teratogenic effects of decitabine when administered early in pregnancy, although genetic causes have not been totally ruled out in this case. The need for more evidence to evaluate the safety of HMA in early pregnancy is of paramount importance. Our patient's case is also an example of fertility preservation following anti-leukemia chemotherapy. Therefore, effective contraception could not be emphasized more during treatment with HMA.

Consent

Verbal informed consent was obtained from the patient for publication of this case report and any accompanying images.

Author's contribution

All authors contributed equally to the production of this manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgement

None.

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