BAOJ Cancer Research & Therapy

Nahla A M Hamed, BAOJ Cancer Res Ther 2018, 4: 1
4: 049

Editorial

# Conflicts Concerning Treatment of Hematologic Malignancies In Pregnancy

***Nahla A M Hamed****

**Faculty of Medicine, Alexandria University, Egypt*

## Abstract

Hematologic malignancies account to 25% of all malignancies in pregnancy. Frequency and localization are comparable to those of non-pregnant woman of the same age**.** This paper presents the challenging in the management of a pregnant patient with malignancy. The therapy of choice of pregnancy-associated cancer should consider drug teratogenicity. It depends on the trimester of exposure, dose, frequency, duration of treatment and the characteristics affecting placental transfer. During the first trimester, avoid chemotherapy or consider abortion if possible. Use of chemotherapy in the second and third trimesters seems to be relatively safe. However, there are case reports of growth restriction, intrauterine and neonatal death, prematurity and myelosuppression. Radiotherapy is possible, if the fetal exposure does not exceed the threshold dose of 10cGy. The decisions in treatment of pregnancy-associated cancer should be approached interdisciplinary and should be individualized for each patient.

**Abbreviation:** ALL- Acute Lymphoblastic Leukemia; AML- Acute Myeloid Leukemia; APL-Acute Promyelocytic Leukemia; AUC- Area Under the Curve; CHOP- Cyclophosphamide, Vincristine, Doxorubicin, Prednisone; CLL- Chronic lymphocytic Leukemia; CMV- Cytomegalovirus; CML- Chronic Myeloid Leukemia; FDG- fluor-2-deoxy-D-glucose; HL- Hodgkin's Lymphoma; NHL- Non-Hodgkin's Lymphoma; NSAID's- Non-Steroidal Anti-Inflammatory Drugs; MRI- Magnetic Resonance Imaging; PET- Positron Emission Tomography Scan; TKI- Tyrosine Kinase Inhibitor

## Introduction

The occurrence of pregnancy-associated malignancy is relatively rare [1]. Cancer is diagnosed in 0.07% to 0.1% of pregnancies and represents the second cause of maternal death after vascular complications. Hematologic malignancies account to 25% of all malignancies in pregnancy [2] behind carcinomas of the breast (26%) and cancer of the uterine cervix (26%) [3]. Frequency and localization are comparable to those of non-pregnant woman of the same age [4]. The most common hematological malignancies during pregnancy are acute leukemia, HL and NHL [5]. The most frequent malignant tumor in women 15 to 24 years of age is HL. It accounts for 51% of the hematologic malignancies complicating pregnancy and is the fourth most common cancer encountered during gestation [3].

### HL

The incidence of HL during gestation is 1:1000 to 1:6000 [3]. Approximately 70% of pregnant patients with HL present with stage I–II disease with 8-year survival rates of 83%. Pregnancy does not affect the disease stage at diagnosis, the response to therapy, or the overall survival rate. In addition, pregnancy termination does not seem to improve maternal outcome [3]. Early stage HL diagnosed in the first trimester should be followed-up at short intervals for signs of disease progression without any treatment until the second trimester [6].Treatment should not be delayed if patient presents with B symptoms, Bulky, sub diaphragmatic, or progressive HD after the first trimester [7]. Patients should be treated with the ABVD-regimen rather than with M-/COPP-regimen; especially during the first trimester [6].

### NHL

Most pregnant women with NHL have aggressive and advanced-stage disease. Those women diagnosed in the first trimester should be offered pregnancy termination. After the first trimester, pregnancy termination is not indicated [3]. CHOP is considered safe in second and third trimester. Rituximab seems safe. Antimetabolites should be avoided in first trimester. No data is available about the safety of M-/VACOP during pregnancy [6].

***Corresponding Author:** Nahla A M Hamed , Hematology, Faculty of Medicine, Alexandria University, Egypt, E-mail: drhamedn@hotmail.com

**Sub Date**: January 18th, 2018, **Acc Date**: Feburary 26th, 2018, **Pub Date**: Feburary 27th , 2018,

**Citation:** Nahla A M Hamed (2018) Conflicts Concerning Treatment of Hematologic Malignancies In Pregnancy. BAOJ Cancer Res Ther 4: 049.

### Leukemia

The incidence of leukemia coincident with pregnancy is 1:75,000 to 1:100,000 (3). A total of 28% of leukemia cases diagnosed during pregnancy are ALL while AML and CML represent the remainder [1].

### AML

AML accounts for more than two-thirds of leukemias during pregnancy [4]. Pregnancy often results in a delay in diagnosis. Diagnosis is generally made during the second (37%) and third (40%) trimester. Only 23% of acute leukemia is diagnosed during the first trimester. Early symptoms are non-specific, such as fatigue, weakness, dyspnea, and pallor which may be attributed to the physiological changes occurring during pregnancy. Recurrent infections and bleeding reflect bone marrow failure. The diagnostic approach includes bone marrow aspiration, immunophenotyping, cytogenetics, and molecular studies [4]. If leukemia is untreated; the patient will have a short life span, a higher probability of spontaneous abortion or fetal death, and a lower probability of a healthy neonate [8]. A strong recommendation for pregnancy termination during the 1st trimester is given. In 2nd and 3rd trimesters treatment with cytarabine and doxorubicin should be instituted promptly [7]. In most pregnant patients, life threatening complications were associated with neutropenia. The frequent complication was acute respiratory failure due to pneumonia caused by pneumocystis jirovecii [9]. For APL in the 2nd and 3rd trimester initiate ATRA with an anthracycline if the leukocyte count is less than 10,000/mm3 and an anthracycline alone if the leukocyte count is greater than 10,000/mm3 to decrease the risk of ATRA syndrome. Arsenic trioxide is teratogenic and contraindicated in pregnancy [7].

### ALL

Chemotherapy is mainly given during the second and third trimester. Chemotherapy regimens mostly include anthracyclines, vincristine and steroids. Some infants were born with few adverse outcomes including transient pancytopenia, respiratory distress and preterm delivery [1]. Methotrexate (folate antagonist) should be avoided [6]**.** In the 3rd trimester treatment protocols as in non-pregnant women must be followed [7].

### CLL

Therapy can usually be delayed until post-partum. If intervention is required leukapheresis could be an option. Autoimmune complications should be managed with corticosteroids as in non-pregnant patients. Chlorambucil is contraindicated during the 1st trimester because of its teratogenicity and its use is not recommended during late pregnancy. Fludarabine must be avoided in pregnancy [7].

### CML

The best advice to all female CML patients in the child bearing period is to use adequate contraception while on TKI treatment, and plan for pregnancy when achieve deep molecular response with close monitoring. Although 40% of patients may lose response following treatment interruption, patients will typically regain response upon resuming treatment. Rarely therapy of any kind is needed during pregnancy [10]. Interferon is the treatment of choice for CML throughout pregnancy. INFα does not cross the placenta to a great extent due to its high molecular weight (19kDa) and does not inhibit DNA synthesis [7]. Pregnancy seems to be not a contraindication for leukapheresis [6]. Imatinib is teratogenic in pregnant rats causing defects such as exencephaly, encephaloceles and deformities of skull bones [6].The concentration of imatinib and its active metabolite were higher in the placenta than in the maternal blood, while they were low or undetected in the umbilical cord. These findings suggest limited placental transfer of imatinib in late pregnancy. It seems that administering imatinib during the first trimester is associated with a considerable risk of congenital anomalies and spontaneous abortions, while late exposure does not have the same impact [7]. It is recommended that patients on second-generation TKI (dasatinib, nilotinib) drugs should avoid pregnancy [7]. Hydroxyurea is capable of crossing the placenta and should be avoided in 1st trimester [7].

## Investigations

### Blood Picture

The physiological changes associated with pregnancy such as anemia of pregnancy, leucocytosis, or gestational thrombocytopenia can mask certain laboratory abnormalities typically present in AML [4].

### Histopathological Examination

Biopsies (lymph node or bone marrow) can safely be performed under local anesthesia [7].

### Diagnostic Medical Imaging

No increase in abortion, growth retardation or congenital malformation from diagnostic exposures below 10cGy (at any time during gestation). Abdominal and pelvic CT should be avoided. Ultrasonography or MRI may provide the desired diagnostic information. Iodinated contrast seems safe to use in pregnancy. FDG can cross the placenta and is not recommended during pregnancy. Limiting the dose of the radiopharmaceutical, supplementary maternal hydration and the use of a bladder catheter is needed when 18F-PET is needed for lymphoma staging [7].

## Treatment of Hematologic Malignancies in Pregnancy

### Supportive treatment

- No association between metoclopramide, anti-histamines or on-dansetron-based anti-emetics and fetal malformations in humans [6].
- Paracetamol can be administered safely throughout pregnancy [6].
- NSAID's are not teratogenic. Their effect on prostaglandins, in third trimester (> 32 weeks), is associated with premature closure of the

ductus arteriosus, oligohydramnios, prolonged gestation and labor [6].

- CMV-negative blood products should be administered during pregnancy regardless of CMV serostatus (Grade 1B) [11].
- There is large data regarding fetal safety of penicillins, cephalosporins and erythromycin. Aminoglycosides seem to be safe in the first trimester on limited data [6]. Quinolones (cause arthropathy), tetracyclines(affect bone and teeth) (Grade 1B) [11] and Trimethoprim-sulfamethazine (higher rate of cardiovascular malformations in the second-third months of pregnancy) should be avoided during pregnancy. Sulfonamides, and other folate antagonists should be avoided due to associated neural tube defects, and cardiac malformations [6]. Amphotericin B or lipid derivatives are the antifungal of choice in pregnancy (Grade 2C) [11].
- Limited evidence suggests that granulocyte colony stimulating factor and erythropoietin is safe to both mother and fetus [6].
- Methylprednisolone and hydrocortisone are extensively metabolized in the placenta. They are therefore preferred over dexa- or betamethasone [6].
- Ultrasound scans should be performed every 2-3 weeks to evaluate the fetal growth, development and well-being [7].
- Elective surgery – under general anesthesia –is safe even during the first trimester [7].

## Chemotherapy

The management of a pregnant patient with malignancy is very challenging and requires a multidisciplinary approach [1]. The main goal will be to come to the end of the pregnancy (> 35-37 weeks) with a viable healthy fetus and newborn and as little impairment as possible to the mother [4]. It is best to avoid chemotherapy during the first trimester to avoid harmful effects to the fetus [1]. The potential fetal effects depend on the gestational age at exposure. During the implantation period (first 10 days after conception) the number of surviving omnipotent stem cells will determine whether a miscarriage occurs, or a normal embryo will develop. Between 10 days and 8 weeks after the conception organogenesis occurs and this period is a risk for congenital malformations. Chemotherapy administration is contraindicated until a gestational age of 10 weeks. Chemotherapy may start from a gestational age of 14 weeks [7]. Use of chemotherapy in the second and third trimesters seems to be safe [6]. Chemotherapy should not be administered after 35 weeks since spontaneous labor becomes more likely [7].

However, if acute leukemia is diagnosed during the first trimester and chemotherapy cannot be avoided, therapeutic abortion should be considered due to increased risks of fetal death, spontaneous abortion or congenital abnormalities [12] If the mother decides to continue the pregnancy and multidrug treatment in first trimester is required, anthracycline antibiotics, vinca alkaloids or single-agent treatment followed by multi-agent therapy after first trimester should be considered [6].

It is recommended that certain drugs should always be avoided, such as folate antagonists, idarubicin and concomitant radiotherapy [5]. Doxorubicin rather than idarubicin or epirubicin should be given. Cytarabine, methotrexate (and other antimetabolites), thioguanine and ATRA should be avoided in first trimester [6]. ABVD, Rituximab, and alfa-Interferon seem to be rather safe in all trimesters of pregnancy. CHOP is safe in second and third trimester. Imatinib should be avoided in all trimesters [6]. During pregnancy the distribution volume (plasma volume expansion by 50%) and clearance were increased and the AUC and Cmax decreased. This assumes that physiological changes of pregnancy result in lower plasma levels of chemotherapeutic agents. This appears to be associated with decreased bone marrow toxicity [6].

A study that includes 84 children who were born to mothers received chemotherapy during pregnancy for hematological malignancies and with a median follow-up of 19 years, did not show any congenital, neurological, immunological and psychological abnormalities including normal learning and educational behavior [7]. However, there are case reports of growth restriction, intrauterine and neonatal death, prematurity and myelosuppression [1]. In a small series, it was suggested that children who were exposed in utero to cytotoxic drugs showed a tendency towards a thinner ventricular wall [6].

## Radiation

Two types of embryonic or fetal damage from radiation may be classified. Firstly, the deterministic radiation effects, such as mental retardation and organ malformations, which arise above a threshold dose of 0.1 – 0.2 Gy in the first 12 weeks of pregnancy, when the embryo is in the stage of organogenesis and the CNS is especially sensitive to radiation. Secondly, the stochastic effects e.g. cancer induction and genetic effects (in the offspring of irradiated individuals).These effects increases with administered dose and manifest many years later ("*late*" effects) [7].

Radiation treatment can be safely given during pregnancy when necessary. Radiation doses used in cancer therapy are usually within the range of 4000-7000 cGy which is more than 1000-fold the level in diagnostic radiology. For embryo doses of 10 cGy, the risk of hereditary effects is negligible. The probability that a child will not develop cancer from ages zero to 19 years is 99.1%. Thus, embryo dose up to 10 cGy should not be considered a reason for pregnancy termination. A distance of over 30 cm from the field edges will yield an exposure of the fetus to 4-20 cGy and therefore areas such as the head, neck and extremities can be treated with radiation without significant fetal exposure. Supplemental fetal-shielding can reduce the fetal exposure by 20% to 60% [6].

## Delivery

If chemotherapy has been given during pregnancy, delivery should be induced or cesarean section performed as near to term as possible [6] at least 2 or 3 weeks after the last chemotherapy to allow maternal/fetal bone marrow recovery and fetal drug excretion via the placenta [12]. Neonates - especially preterm babies - have limited capacity to metabolize and eliminate drugs due to liver and renal immaturity [7]. Chemotherapy can be restarted when needed after delivery. An interval of one week after an uncomplicated cesarean section is required [7].

A course of corticosteroids should be considered if delivery is anticipated between 24 and 35 weeks gestation, given over a 48-h period during the week prior to delivery (Grade 1A). Use of magnesium sulphate should be considered in the 24 h prior to delivery if this is before 30 weeks gestation (Grade 1A). Epidural analgesia should be avoided in a woman who had platelet count <80 x $10^9$/l and/or white blood cell count <1 x $10^9$/l: (Grade 1C). Antibiotics should be administered during and after premature rupture of membranes and delivery (Grade 1C) [11].

Breastfeeding is contra-indicated if the mother is receiving or has recently received chemotherapy [6].

## Placental Issues

### Transplacental Transfer of Chemotherapy

Only a few case reports of transplacental transfer of chemotherapy in humans are available. Transfer mainly occurs by passive diffusion, but also active transporters like P-glycoprotein, Multidrug Resistance Proteins and Breast Cancer Resistance Protein have an important role in the regulation of the placental drug transfer. A baboon model showed significant levels of platinum in fetal plasma samples after intravenous carboplatinum administration, but lower levels of doxorubicin, epirubicin,paclitaxel, vinblastine, and 4-OH-cyclophosphamide. Docetaxel was not detected in fetal samples [7].

### Placental Metastases

are rare; some previous reports demonstrate trans-placental cancer transmission from mother to fetus [12]. A maternal case of T-cell NHL, developing in the infant at 2 months of age and a case of anaplastic large cell lymphoma metastatic to the placenta have been reported [3]. Histological examinations of the placenta and the umbilical cord should be performed to assess leukemic cell infiltration [12] so that appropriate and timely consideration for neonatal follow-up and treatment can be effected [3].

## Conclusion

The management of a pregnant patient with malignancy is very challenging and requires a multidisciplinary approach. The main goal will be to come to the end of the pregnancy with a viable healthy newborn with little or no impairment to the mother.

## References

1. Ticku J, Oberoi S, Friend S, Busowski J, Langenstroer M, et al. (2013) Acute lymphoblastic leukemia in pregnancy: a case report with literature review. Ther Adv Hematol 4(5): 313–319.
2. Cabrera-Garcia A, Vargas-Trujillo S, Hernandez-Company A, Balderos-Delgado C, Dias-Vargas G, et al.( 2017) A multicenter retrospective experience of hematologic neoplasms in pregnancy. Blood 130: 4716.
3. Hurley TJ, McKinnell JV, Irani MS (2005) Hematologic malignancies in pregnancy. Obstet Gynecol Clin N Am 32(4): 595– 614.
4. Thomas X (2014) Acute myeloid leukemia in the pregnant patient. European Journal of Haematology 95: 124–136.
5. Aviles A, Neri N, Nambo M-J (2012) Hematological malignancies and pregnancy: Treat or no treat during first trimester. Int J Cancer 131(11): 2678–2683.
6. Vandenbriele C, Dierickx D, Amant F, Delforge M (2010) The treatment of hematologic malignancies in pregnancy. Ob Gyn 2 (2): 74-87.
7. Vandenbriele C, Vassou A, Pentheroudakis G, Van Calsteren K, Amant (2011) F Hematologic malignancies in pregnancy. In: Antica M (ed).Acute Leukemia – The Scientist's Perspective and Challenge. InTech: 371-390.
8. Chang A, Patel S (2015) Treatment of acute myeloid leukemia during pregnancy. Annals of Pharmacotherapy 49(1): 48–68.
9. Bazhenov A, Galstian GM, Troitskaa VV, Parovichnikova EN, Makhina S,Drokov YM, et al. (2016) Outcome of pregnant women with acute leukemia treated for life-threatening complications. Blood128: 5976.
10. Assi R, Kantarjian HM, Keating MJ, Pemmaraju N, Verstovsek S, Garcia- Manero G, et al. (2017) Management of chronic myeloid leukemia (CML) during pregnancy among patients treated with a tyrosine kinase inhibitor: a single-center experience. Blood; 130: 2881.
11. Ali S, Jones GL, Culligan DJ, Marsden PJ, Russell N, Embleton ND, et al. (2015) on behalf of the British Committee for Standards in Hematology. Guidelines for the diagnosis and management of acute myeloid leukemia in pregnancy. British Journal of Haematology 170: 487–495.
12. Nakajima Y, Hattori Y, Ito S, Ohshima R, Kuwabara H, Machida S, et al. (2015) Acute leukemia during pregnancy: an investigative survey of the past 11 years. Int Jnl Lab Hem 37: 174–180.