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REVIEW

Non-Hodgkin lymphomas in pregnancy: Tackling therapeutic quandaries

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ABSTRACT

Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) often present with systemic symptoms such as fatigue, shortness of breath and night sweats, mimicking pregnancy-related features which may result in delayed disease diagnosis. Furthermore, the wish to avoid investigational imaging, aiming to protect the fetus from radiation exposure, may lead to a further delay, which does not often result in significant changes in HL clinical nature and patient outcome. In contrast, a more aggressive behavior (i.e., advanced disease stage and reproductive organ involvement) of most NHL types diagnosed in pregnancy may require urgent therapeutic intervention to prevent disease progression.

Current management of pregnancy-associated NHL depends on histological subtype of the disease, gestational stage at diagnosis and the urgency of treatment for a specific patient. Patients diagnosed with indolent lymphoma may often be just followed, whereas those presenting with aggressive or highly aggressive disease need to be urgently treated with chemoimmunotherapy, either after undergoing an elective pregnancy termination if diagnosed at an early gestational stage, or with pregnancy preservation, if diagnosed later.

Supportive care of NHL is also important; however, granulocyte colony stimulating factor (G-CSF) which is commonly used outside of pregnancy, should be cautiously employed, considering its established teratogenicity in animals, though this is less proven in humans. In conclusion, given the paucity of studies prospectively evaluating the outcome of pregnant women with NHL, international efforts are warranted to elucidate critical issues and develop guidelines for the management of such patients.

1. Introduction

The diagnosis of lymphoma during pregnancy is a stressful event, associated with major ethical and medical dilemmas for the pregnant woman, her family and the medical team. In this situation, the need to treat a patient for a potentially lethal disease using aggressive chemotherapy is to be balanced with the necessity to avoid therapy-related teratogenic and other side effects on the fetus.

Current recommendations for the management of both Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) are based on case studies and relatively small series, due to the rarity of this disease, estimated to involve 1 out of 6000–10,000 pregnancies [1–6].

Pregnancy-associated HL appears to exhibit features and outcome similar to those reported in the disease occurring outside of pregnancy [7,8], whereas pregnancy-associated NHL (PA-NHL) is characterized by a more aggressive nature. PA-NHL commonly involves reproductive organs (i.e., breast, cervix, ovary, placenta) and presents at an advanced disease stage, which may at least partly explain the inferior outcome often reported in these patients compared to their non-pregnant counterparts [9].

Delayed diagnosis attributed to “misleading” symptoms (e.g., progressive weakness, shortness of breath),“incorrectly” interpreted as pregnancy-related physiological changes, along with unwillingness to perform imaging scans during pregnancy, aiming to avoid fetal exposure to radiation, may also contribute to the unsatisfactory outcome often reported in these women.

The optimal therapy for lymphoma occurring during pregnancy has not been established. Multiple physiological changes observed in pregnancy, including increased plasma volume and renal clearance, hepatic oxidation, and accumulating amniotic fluid, can affect drug distribution, metabolism, and excretion [10,11]. Plasma and tumor concentrations of various chemotherapeutic agents may be reduced during pregnancy; however, pharmacokinetic data from studies of pregnant women are limited [12]. Given pregnancy-associated changes in bio-distribution of chemotherapeutic agents, higher dosages might be required to achieve optimal therapeutic blood levels.

The current review, presenting cases of women, diagnosed with NHL in pregnancy, addresses the challenging therapeutic issues involved, with a special focus on optimal treatment strategies.

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Case 1. Diffuse large B cell lymphoma.

A 33-year old previously healthy woman presented with an enlarged right supraclavicular lymph node and constitutional symptoms, at week 15 of her first pregnancy.

A true-cut biopsy showed diffuse large B-cell NHL. MRI of the neck, chest, abdomen, and pelvis revealed enlarged lymph nodes involving the mediastinum and the left supraclavicular area. Bone marrow biopsy (BM) demonstrated marked infiltration with lymphoma cells. Her hemoglobin level was 11.0 g/dL, whereas results of all other laboratory tests, including lactate-dehydrogenase (LDH) blood level, were within normal range. The patient was diagnosed with low International Prognostic Index (IPI), stage IVB diffuse large B cell (DLBCL) NHL. Potential risks associated with chemotherapy administration to the mother and the fetus were thoroughly discussed with the woman and her husband and they decided to continue pregnancy with concomitant anti-lymphoma therapy. Six cycles of the CHOP-R regimen were administered with no side effects and she delivered a healthy baby at week 36 of pregnancy. Two cycles of high-dose methotrexate (MTX) were given after delivery. PET-CT after completion of chemotherapy was consistent with complete remission.

Questions:

This case, presenting a woman diagnosed with stage IV symptomatic DLBCL during the second trimester of pregnancy, raises the following major questions:

(a) What are the most common subtypes of NHL occurring during pregnancy and what are the typical clinical features of pregnancy-associated aggressive NHL?
(b) Is it really feasible and important to perform a lymph node and bone marrow biopsy during pregnancy?
(c) Which imaging techniques are permitted and recommended during the first trimester of pregnancy and beyond?
(d) What is the optimal management of DLBCL during pregnancy, including the employment of anti-CD20 monoclonal antibodies?

2. Case discussion

2.1. Clinical features of pregnancy-associated aggressive NHL

The diagnosis of aggressive NHL during pregnancy is very rare and hard to be accurately established .

A recent multicenter retrospective analysis, evaluating 50 patients diagnosed with lymphoma during pregnancy, found that almost all cases of NHLs (76%) were of an aggressive type, specifically, DLBCL (56%) or T cell lymphoma (20%). Stages III–IV NHL at diagnosis appeared to be common (40%) and extra-nodal disease was frequently identified, with 26% of patients having more than one extra-nodal site. Notably, several atypical sites were observed [8].

Of interest, the proportion of cases with reproductive organ involvement was remarkably high compared to that reported in non-pregnant women with NHL [9,13]. In the majority of patients, reproductive organ involvement was biopsy-proven. The most commonly affected organs appeared to be the breast followed by the ovary and the uterus. This unique phenomenon may result from increased blood flow to these organs, as well as the estradiol-progesterone induced immunosuppression [14–23]. Moreover, healthy B-lymphocytes are functionally regulated by sex hormones [24]; therefore, enhanced expression and/or activation of sex hormone receptors on malignant lymphocytes, may theoretically play a role.

2.2. Lymph node and bone marrow biopsy performed during pregnancy

In the presence of sustained unexplained lymphadenopathy, even without B symptoms, lymph node biopsy is required to rule out lymphoma or to define its histological subtype, given the need for immediate intervention in case of aggressive lymphoma [7,8]. Accumulating data confirm the feasibility and safety of core and even excisional lymph node biopsy during pregnancy, including early gestational stages [10,25,26].

2.3. Challenges of imaging during pregnancy

Staging of DLBCL in non-pregnant patients is based on findings of computer tomography (CT) [27,28] or positron emission tomography (PET-CT) scan [27–30], visualizing the chest, abdomen and pelvis. However, both techniques are potentially fetotoxic, especially if employed at early gestational stages [31,32]. Their use may increase the risk of teratogenicity and carcinogenesis. The threshold for radiation-related mental retardation is estimated within the range of 20–40 rads [33,34], while the risk of fetal anomalies, growth restriction and early abortions is not increased with radiation exposure of less than 5 rads [35]. It is estimated that fetal exposure to 1–2 rads may increase the risk of leukemia by a factor of 1.5–2 over the natural incidence, i.e., 1 in 2000 children exposed to in utero radiation will develop childhood leukemia [35]. Therefore, alternative procedures, including abdominal/pelvic ultrasound or magnetic resonance imaging (MRI) in combination with chest X-ray, are often applied [36]. Table 1 and Box 1 summarize the data regarding estimated fetal exposure to radiation during imaging scans and current recommendations for performing these tests at different gestational stages.

The recommended treatment for low IPI DLBCL is 6 cycles of the CHOP-R-regimen (i.e., every 21 days). For stage I disease, 4 CHOP-R cycles followed by localized radiotherapy to the involved area are acceptable. For high IPI DLBCL, outside of a clinical trial, 6–8 cycles of the CHOP-R regimen or even a more intensive therapy with or without CNS prophylaxis are recommended [27,28].

2.4. Chemotherapy during the first trimester of pregnancy

Most cytotoxic drugs have a molecular weight between 250 and 400 kDa and can easily cross the placenta [37]. In contrast to studies on animal models where single agents were used, data related to chemotherapy applied during human pregnancy mostly originate from reports and studies employing multi-agent regimens, which complicate reliable estimation of specific drug effects. The fetus is most vulnerable to drug-related teratogenicity during organogenesis (the first 2–8 weeks of gestation) [38]. Thus, usually DLBCL requires immediate treatment and the exact timing of its diagnosis during pregnancy is critical. The use of an anthracycline-containing regimen during the first trimester was shown to interfere with eye and limb development [39]; therefore, termination of pregnancy is highly recommended before administrating definitive anti-lymphoma therapy (Table 2).

If a symptomatic DLBCL is diagnosed late in the first trimester (i.e., after week 10) a single course of cyclophosphamide and corticosteroids could be given while the full anthracycline regimen is to be postponed until week 12 when the risk of congenital malformations is significantly lower. If a patient is asymptomatic, therapy should be deferred until the beginning of the second trimester.

2.5. Chemotherapy during the second and third trimesters of pregnancy

Administration of chemotherapy during the second and third trimesters is not associated with a significant increase in the risk of congenital malformations. However, there is an elevated risk for intrauterine growth retardation (IUGR), pre-term delivery and low birth weight [40]. Several case reports described the use of the CHOP-R regimen after the first trimester of pregnancy, showing a good clinical outcome for the mother and the fetus [41–43].

Data regarding prevalence of cardiomyopathy attributed to anthracycline administration during the second or third trimesters are controversial [44–46]. Although this observation is based on quite