RESEARCH LETTER

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TO THE EDITOR:

Treatment of primary mediastinal B-cell lymphoma with dose-adjusted REPOCH during pregnancy

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Cancer during pregnancy is uncommon, occurring in ~1 per 1000 pregnancies annually. Lymphoma is the fourth most common malignancy associated with pregnancy, after melanoma, breast cancer, and cervical cancer.[1] Non-Hodgkin lymphoma diagnosed during pregnancy usually tends to be of a more aggressive subtype.[2] The management of primary mediastinal B-cell lymphoma (PMBCL) includes DA-REPOCH (dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), which demonstrated superior outcomes (5-year overall survival rate was 97%) in the single arm phase 2 study from the national cancer institute obviating the need for radiation therapy (XRT).[3] Alternatively, R-CHOP alone or with consolidation XRT is also used for the management of PMBCL, although the latter is preferred given the survival benefit associated with the XRT consolidation,[4] pending the results of phase 3 randomized study looking into the role of consolidation XRT (NCT01599559) following rituximab-containing chemotherapy regimens.

The treatment of lymphoma during pregnancy can be challenging. Caring for a pregnant patient with a malignancy requires striking the difficult balance between treating the mother and, at the same time, minimizing possible harm to the fetus.[5,6] Antenatal treatment is largely based on case reports and small case series. A multicenter analysis of treatment outcomes for pregnant patients with Non-Hodgkin lymphoma only included 1 patient treated with DA-REPOCH.[7] There are reports of patients with PMBCL treated with R-CHOP during pregnancy and then transitioning to DA-REPOCH post partum.[8] This was done due to the concern that etoposide would cause fetal cranial abnormalities and skeletal malformations. However, etoposide exposure during the second and third trimesters did not seem to cause any congenital malformations.[9-12] Some have suggested withholding rituximab during pregnancy due to its lymphodepleting effect and increased risk of fetal infection.[13,14] Herein, we report a case series describing the efficacy and safety of DA-REPOCH administered to 4 antepartum women with PMBCL.

This is a single-institution retrospective study that included adult pregnant patients treated with DA-REPOCH chemotherapy from 2010 to 2022. The study was approved by the Institutional Review Board and was performed per the Declaration of Helsinki.

We identified 4 patients with PMBCL who received DA-REPOCH during pregnancy through a review of medical records. Information regarding the delivery and any neonatal complications was obtained by reviewing the mothers' charts. Key patient and infant characteristics are listed in Table 1. All patients received chemotherapy (all cycles) as inpatients, except patient 3, who received only the first cycle (C1) as an inpatient and the rest as an outpatient.

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For data sharing, contact the corresponding author, Narendranath Epperla (Narendranath.Epperla@osumc.edu).

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Table 1. Salient features of the pregnant patients treated with DA-REPOCH during the antepartum period

Case	Age at Dx (y)	Initial presentation	Initial WBC (k/μL)	Initial Hgb (g/dL)	Initial PLT (k/μL)	LDH (U/L) ULN >190	R-IPI	Staging studies	Highest dose escalation	Weeks pregnant at Dx	Gestational weeks at the start of therapy	Weeks at delivery	Weight of baby at delivery (lbs)	APGAR Score at delivery (out of 10)	NICU	Response to treatment	Months in remission at last follow-up
Case 1	33	SOB; chest pain	13.43	11.7	261	752	1	MRI A/P, CT chest, BMBx	2	20	20w 5d	37w 5d	5.71	8	No	CR	35.2
Case 2	36	Left thigh pain and swelling	14.5	9.6	496	958	3	CT chest, MRI A/P, BMBx	3	17	18	37w 5d	7.56	8	No	CR	63.3
Case 3	26	SOB; facial swelling	8.46	10.1	431	648	Unable to calculate	CT chest	3	30	31	36w 3d	5.16	8	No	CR	17.9
Case 4	39	SOB; dyspnea on exertion	7.63	11.1	267	233	Unable to calculate	CT chest, MRI A/P	3	15	16	35w 3d	5.29	8	Yes	CR	7.4

A/P, abdomen and pelvis; APGAR, appearance, pulse, grimace, activity, respiration; BMBx, bone marrow biopsy; CR, complete response; hgb, hemoglobin; LDH, lactate dehydrogenase; NICU, neonatal intensive care unit; plt, platelet; R-IPI, revised international prognostic index; SOB, shortness of breath; WBC, white blood cell.

Case 1

A 33-year-old G4P2 female presented at 20 weeks gestation to the emergency department (ED) for shortness of breath (SOB) and chest pain. She had a computerized tomography (CT) chest with shielding that was notable for a large anterior mediastinal mass. She underwent a core needle biopsy that demonstrated PMBCL. Staging studies included an MRI abdomen, pelvis, and bone marrow biopsy. Her ECOG performance status was 1 with a revised international response index[15] risk score of 1. C1 of DA-REPOCH was initiated shortly after diagnosis at 20 weeks and 5 days. As the patient was diagnosed with left internal jugular (IJ) thrombus before initiation of treatment, central access was obtained through the right IJ. She experienced no treatment delays with grade 1 to 2 mucositis being the only reported adverse effect. She completed 6 cycles at 35 weeks gestation. She was induced at 37 weeks and 5 days after presenting to the maternal-fetal medicine clinic with new-onset hypertension. There were no complications during delivery. The baby, weighing 5.71 lbs, did not suffer any complications and was discharged home with the mother. Posttreatment PET showed complete response (CR), and has been in remission for over 35 months at the last clinic follow-up.

Case 2

A 36-year-old G3P2 female presented at 17 weeks gestation with left thigh pain related to a soft tissue mass. She underwent an ultrasound-guided core biopsy of the thigh mass that was reported as diffuse large B-cell lymphoma. Her workup included an MRI abdomen and pelvis along with a CT chest with shielding. The CT chest showed a 12 cm mediastinal mass, and she was categorized as advanced-stage PMBCL. She started DA-REPOCH at 18 weeks through a right arm peripherally inserted central catheter (PICC) line. Her treatment course was complicated by worsening malignant pericardial effusion and pericarditis following C1 (improved with steroids) and mucositis following C4. She completed 6 cycles of treatment at 36 weeks and 6 days gestation. She had a spontaneous vaginal delivery at 37 weeks and 5 days without any complications during delivery. The baby, weighing 7.56 lbs, did not suffer any complications and was discharged home with the mother. Posttreatment PET showed CR, and has been in remission for over 63 months at the last clinic follow-up.

Case 3

A 26-year-old G3P2 female presented to the ED with SOB and facial swelling at 30 weeks gestation. A CT chest demonstrated a large anterior mediastinal mass with associated pericardial effusion, superior vena cava occlusion, compression of the trachea, and proximal right mainstem bronchus. She underwent pericardial window and anterolateral thoracotomy with pathology consistent with PMBCL. Her ECOG performance status was 2. Staging studies were not completed due to her tenuous clinical status. She began treatment with DA-REPOCH at 31 weeks in the intensive care unit (ICU). She completed 2 cycles of chemotherapy before a preterm (vaginal) delivery at 36 weeks 3 days without any maternal or fetal complications during delivery. The baby weighed 5.16 lbs on delivery without any complications following delivery. The baby was discharged home

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with the mother. She restarted chemotherapy following the delivery and received C3 DA-REPOCH 1-week post partum. Due to incomplete staging limiting the estimation of risk for central nervous system recurrence, the decision was made to start intrathecal methotrexate prophylaxis before C4. However, the patient developed intractable headaches related to the lumbar puncture resulting in the delay of the C4 DA-EPOCH. She did not receive further lumbar puncture/intrathecal chemotherapy. She experienced grade 2 peripheral (sensory predominant) neuropathy and grade 2 mucositis with treatment. She was also found to have an occlusive right IJ thrombus during treatment that resulted in PICC removal and tunneled femoral line placement before C5. Posttreatment PET showed CR. She has been in remission for 18 months at the last clinic follow-up with the resolution of peripheral neuropathy.

Case 4

A 39-year-old G2P0 female presented at 15 weeks gestation to the ED with SOB and dyspnea on exertion. A CT angiogram revealed a large mediastinal mass, and she underwent an ultrasound-guided left supraclavicular lymph node biopsy, which came back as PMBCL. The patient had been deemed at high risk for obstetric complications before her lymphoma diagnosis due to advanced maternal age and opioid use. She started DA-REPOCH through right arm PICC line at 15 weeks and 3 days and completed 6 cycles before delivery at 31 weeks. The patient had a premature rupture of membranes that necessitated a cesarean section at 35 weeks and 3 days with preterm delivery. Her postpartum course was complicated by preeclampsia. The infant, who weighed 5.29 lbs on delivery, was in the neonatal ICU (NICU) for 5 days due to the premature delivery as well as monitoring for neonatal abstinence syndrome. The baby did not experience any complications while in the NICU and was subsequently discharged. Posttreatment PET showed CR. She did not experience any lasting adverse effects from treatment and has been in remission for 7 months at the last clinic follow-up.

Although, there has been no randomized study comparing the outcomes of DA-REPOCH vs R-CHOP +/− XRT in patients with PMBCL, the decision to use either of the treatment modalities needs to be individualized weighing the risks and benefits. At our center, all patients with PMBCL, including those who are pregnant, are treated with DA-REPOCH given the excellent survival outcomes associated with this regimen as well as the ability to avoid XRT. Although DA-REPOCH can be associated with increased toxicity compared to R-CHOP,[16] the long-term benefits outweigh the immediate risks in patients with PMBCL including those with pregnancy. Moreover, similar to R-CHOP,[17] DA-REPOCH is relatively safe beyond the first trimester and was not associated with any teratogenic effects in our study.

In our study, we showed that DA-REPOCH can safely be given to patients during their second or third trimester resulting in excellent response rates with an acceptable safety profile for the mother and fetus. Maternal complications included 1 patient who had premature rupture of membranes with preterm delivery at 35 weeks and 3 days and postpartum preeclampsia and another patient with preterm delivery at 36 weeks and 3 days. There were no instances of febrile neutropenia, and all patients received G-CSF support. Fetal complications included 1 baby who required NICU admission for neonatal abstinence syndrome and 3 babies with low birth weight (less than 5.5 lbs). However, there were no infectious complications to the fetuses immediately at postpartum. In the patient who received chemotherapy following delivery (case 3), there was no reduction in the R-EPOCH dose.

Although malignancy makes the pregnancy high risk, it is also important to consider other factors that can increase this risk. Of the 4 patients included in the current case series, only 1 had a birth which resulted in the baby needing NICU-level care. However, this patient had other high-risk factors including advanced maternal age and a history of opioid use.

As patients can manifest life-threatening symptoms at diagnosis, delaying treatment until a patient is postpartum is not feasible and not recommended. While treatment should not be delayed, chemotherapy is usually avoided near the time of delivery due to the theoretical risk of maternal myelosuppression and the risk of active metabolites in the fetus at delivery. As malignancy during pregnancy can be high risk, the management of these patients requires a multidisciplinary approach involving maternal and fetal medicine experts who should monitor patients closely along with the treating oncologist to determine the optimal timing for delivery. The overarching goal, however, should be trying to take the pregnancy as close to the full term as possible,[18] which was the goal in all the patients in our study.

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