Clinical Case Report

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Study on the adverse effects following chemotherapy for breast cancer diagnosis during pregnancy

The first case report in China

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Abstract

Rationale: Treatment of breast cancer during pregnancy (BCP) remains a challenge to physicians. Surgery and chemotherapy during pregnancy are widely used for the treatment of BCP. Herein, we reported 3 Chinese patients with BCP who underwent chemotherapy during pregnancy and were followed up for adverse effects.

Patient concerns: Three female patients (case 1, case 2, and case 3) of 37-, 32-, and 28-year-old with breast masses were enrolled. Case 1 had been pregnant for over 4 months, case 2 over 7 months, and case 3 for 7 months. Ultrasound findings revealed a mass in the left breast in cases 1 and 2 (30 mm × 26 mm × 23 mm and 34 mm × 16 mm × 40 mm), and case 3 had 2 masses in the outer upper quadrant of right breast (27 mm × 27 mm × 26 mm, 18 mm × 17 mm × 17 mm) and 2 fixed enlarged lymph nodes in the right axillary fossa, respectively.

Diagnoses: All breast masses were diagnosed by core needle biopsy, and the result was infiltrating ductal carcinoma.

Interventions: Chemotherapy regimen administered during pregnancy was EwP (epirubicin 80 mg/m^2, d1 + paclitaxel 80 mg/m^2, d1, 8, 15, and cycled every 21 days). During pregnancy, case 1 received 5 cycles, case 2 received 1 cycle, and case 3 received 2 cycles.

Outcomes: Case 2 patient experienced grade III bone marrow suppression once. Electrocardiogram (ECG) result of case 3 showed occasional occurrence of ventricular premature beats, with no complaint of discomfort. All 3 patients experienced uterine contractions, which caused preterm labor in case 2. Adverse events were nausea, hair loss, acid reflux, and constipation. Neonatal jaundice occurred in the premature infant (case 2), which was resolved by phototherapy. No relapse or metastasis was observed in the 3 cases and the infants are growing normally.

Lessons: Both patients and infants well tolerated the combination chemotherapy of epirubicin and paclitaxel during pregnancy. There were few drug toxicities and adverse effects.

Abbreviations: BCP = breast cancer during pregnancy, CNB = core needle biopsy, ECG = electrocardiogram, ER = estrogen receptor, ESMO = European Society for Medical Oncology, HER2 = human epidermal growth factor receptor 2, IDC = infiltrating ductal carcinoma, IHC = immunohistochemical, PR = progesterone receptor.

Keywords: breast cancer, chemotherapy, children, pregnancy

1. Introduction

Breast cancer diagnosed during pregnancy (breast cancer during pregnancy [BCP]) is reported to be delayed by 1–3 months, owing to the physiological changes that occur in the breast during pregnancy. These changes have a proliferative effect on glandular and ductal tissues.[1] However, postponing the treatment in order to continue the pregnancy may result in the progression of cancer. At present, multiple clinical trials and breast cancer practice guidelines, including European Society for Medical Oncology (ESMO) clinical practice guidelines and the National Comprehensive Cancer Network, suggest that exposure to chemotherapy is feasible and safe during pregnancy, only 2nd and 3rd trimesters.[2–6] Chemotherapy is used widely during pregnancy, but there are no reports in China till date. This novel study in China was designed to explore the drug toxicity, adverse effects, and tolerance following chemotherapy in Chinese BCP patients. Ethical approval was given by the medical ethics committee of the International Peace Maternity and Child Health Hospital of China Welfare Institute, and all the participants provided written informed consent.

2. Case report

2.1. Case 1

A 37-year-old female patient who had been pregnant for over 4 months was admitted to our hospital on August 5, 2014 with a

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Table 1

Clinical features, clinicopathologic characteristics, and adverse effects of 3 patients.

	Case 1	Case 2	Case 3
Age	37-year-old	32-year-old	28-year-old
GA at diagnosis	15 wk and 5 d	27 wk and 1 d	29 wk and 3 d
Ultrasound findings			
Mass size	30 mm × 26 mm × 23 mm	34 mm × 16 mm × 40 mm	27 mm × 27 mm × 26 mm, 18 mm × 17 mm × 17 mm
Location of the mass	Upper of left breast	Upper of left breast	Outer upper quadrant of right breast
Bilateral axillary LN	NE	NE	Fixed of two lymph nodes
Diagnosis from CNB			
Histopathologic type	IDC	IDC	IDC
ER	Negative	30%+	Negative
PR	Negative	40%+	Negative
HER2	Negative	1+	Negative
Ki67	10%+	40%+	90%+
Bilateral axillary LN	–	–	Metastases
cTNM	T2N0M0	T2N0M0	T2N2M0
Treat modality	Neo-chemo → delivery → adjuvant treatments	Neo-chemo → delivery → adjuvant treatments	Neo-chemo → delivery → adjuvant treatments
Evaluation after delivery	No distant metastases	No distant metastases	No distant metastases
Postoperative pathology			
Hhistopathologic types	No tumor cell	IDC	IDC
pT	–	20 mm	15 mm
ER	–	80%++	Negative
PR	–	80%++	Negative
HER2	–	2+	Negative
Ki67	–	60%+	95%+
Axillary LN metastases	0/20	2/15	0/18
pTNM	–	T1N1M0	T1N0M0
Postoperative evaluation	pCR	pPR	pPR
AE of mother			
Hematological toxicity	NO	Grade III bone marrow suppression	NO
Hepatic toxicity	NO	NO	NO
Nephrotoxicity	NO	NO	NO
ECG	Normal	Normal	Occasional occurrence of ventricular premature beats for one time without complaint of discomfort
Pregnancy-induced hypertension/eclampsia	NO	NO	NO
AE of infant	NO	Neonatal jaundice due to spontaneous preterm delivery	NO

AE = adverse events, CNB = core needle biopsy, cTNM = clinical TNM stages, ECG = electrocardiogram, ER = estrogen receptor, GA = gestational age, HER2 = human epidermal growth factor receptor 2, LN = lymph node, NE = no enlargement, Neo-chemo = neoadjuvant chemotherapy, NO = not observed, pCR = pathologic complete response, PR = progesterone receptor, pPR = pathologic partial response, pT = pathologic tumor size, pTNM = pathologic TNM stages.

complaint of "left breast mass for 2 months". Ultrasound findings revealed a mass in the left breast (30 mm × 26 mm × 23 mm) and no enlargement of bilateral axillary lymph nodes. Pathological findings of core needle biopsy (CNB) indicated grade II infiltrating ductal carcinoma (IDC), while immunohistochemical (IHC) findings showed estrogen receptor (ER)(−), progesterone receptor (PR)(−), human epidermal growth factor receptor 2 (HER2)(−), and Ki67 (10%+) and the results were presented in Table 1. The patient received therapeutic regimen, including 5 cycles of neoadjuvant chemotherapy during pregnancy, delivery, 1 cycle of neoadjuvant chemotherapy after delivery, and then modified radical mastectomy. Chemotherapy regimen used was EwP (epirubicin 80 mg/m^2, d1 + paclitaxel 80 mg/m^2, d1, 8, 15, cycled every 21 days). The specific therapeutic process used in the study was presented in Table 2.

2.2. Case 2

A 32-year-old female patient who had been pregnant for over 7 months was admitted to our hospital on January 6, 2015 with a complaint of "left breast mass for 1 week." Ultrasound findings demonstrated a mass in the left breast (34 mm × 16 mm × 40 mm) and no enlargement of bilateral axillary lymph nodes. Diagnosis by CNB indicated grade II IDC, while IHC findings showed ER (30%+), PR(40%+), HER2(1+), and Ki67(40%+) (Table 1). The patient received therapeutic regimen, including 1 cycle of neoadjuvant chemotherapy during pregnancy, delivery, 3 cycles of neoadjuvant chemotherapy after delivery, then modified radical mastectomy and 4 cycles of adjuvant chemotherapy and endocrine therapy. Similar to case 1, the neoadjuvant chemotherapy used during pregnancy was EwP (Table 2).

After delivery, neoadjuvant chemotherapy was adjusted to TAC (docetaxel 75 mg/m^2 + doxorubicin 50 mg/m^2 + cyclophosphamide 500 mg/m^2, d1, cycled every 21 days).

Postoperative pathologic diagnosis showed a grade III IDC and axillary lymph nodal metastases. The IHC findings indicated ER (80%++), PR(80%+++), HER2(2+), and Ki67(60%+). HER2(−) and HER2(1+) indicated by IHC findings define as HER2-negative. HER2(3+) indicated by IHC findings define as HER2-positive. HER2(2+) indicated by IHC findings is equivocal result.

Table 2

Therapeutic process of 3 patients.

	Case 1	Case 2	Case 3
GA at diagnosis	15 wk and 5 d	27 wk and 1 day	29 wk and 3 d
GA of 1st neo-chemo	17 wk and 5 d	29 wk	31 wk and 3 d
Cycles of neo-chemo before delivery	5 cycles	1 cycle	2 cycles
GA of delivery	39 wk	32 wk (spontaneous preterm delivery)	37 wk and 4 d (iatrogenic caesarean section for purpose of treatment)
Evaluation after delivery	cPR no distant metastases	cPR no distant metastases	cPR no distant metastases
Cycles of neo-chemo after delivery	1 cycle	3 cycles	2 cycles
Ultrasound findings			
Baseline			
Mass	30 mm × 26 mm × 23 mm	34 mm × 16 mm × 40 mm	27 mm × 27 mm × 26 mm, 18 mm × 17 mm × 17 mm
LN	NE	NE	45 mm × 27 mm, 26 mm × 22 mm
1st evaluation	cPR	cPR	cSD
Mass	19 mm × 20 mm × 12 mm	22 mm × 8 mm × 15 mm	22 mm × 14 mm, 11 mm × 8 mm,
LN	NE	NE	8 mm × 13 mm
2nd evaluation	cPR	cPR	cPR
Mass	17 mm × 19 mm × 9 mm	26 mm × 14 mm × 7 mm	19 mm × 11 mm, 5 mm × 5 mm
LN	NE	NE	10 mm × 7 mm
3rd evaluation	cPR		
Mass	8 mm × 4 mm		
LN	NE		
Operation	MRM	MRM	MRM
Postoperative evaluation	pCR no tumor cells, LN 0/20	pPR pT 2 cm, LN 2/15	pPR pT 1.5 cm, LN 0/18
Postoperative therapy	No	Chemotherapy, endocrine therapy	Chemotherapy, radiotherapy

cPR = clinical partial response, cSD = clinical stable disease, GA = gestational age, LN = lymph node, MRM = modified radical mastectomy, NE = no enlargement, Neo-chemo = neoadjuvant chemotherapy, pCR = pathologic complete response, pPR = pathologic partial response, pT = pathologic tumor size.

The fluorescence in situ hybridization (FISH) assay could identify whether HER2 is positive or negative. However, the FISH assay was not performed due to patient's economic difficulty, so that we could not decide whether trastuzumab should be given to this patient for adjuvant treatment. Trastuzumab is a targeted drug for the treatment of HER2-positive patients.

2.3. Case 3

A 28-year-old female patient who had been pregnant for 7 months was admitted to our hospital on October 12, 2015 with a complaint of "right breast masses for 4 months". Ultrasound findings showed 2 masses in the outer upper quadrant of right breast (27 mm × 27 mm × 26 mm, 18 mm × 17 mm × 17 mm) and 2 fixed enlargement lymph nodes in the right axillary fossa. CNB indicated an IDC, while IHC findings showed ER(−), PR(−), HER2(−), and Ki67 (90%+). Results from the aspiration biopsy demonstrated the right axillary lymph nodes, and pathological examination indicated adenocarcinoma. Abdominal ultrasound showed no liver metastasis. Cancer was staged as cT2N2M0 (Table 1). The patient received therapeutic regimen, including 2 cycles of neoadjuvant chemotherapy during pregnancy, delivery, 2 cycles of neoadjuvant chemotherapy after delivery, then modified radical mastectomy and 12 cycles of adjuvant chemotherapy and radiotherapy. The neoadjuvant chemotherapy used during pregnancy and after delivery were the same as those for case 1 EwP (Table 2). After operation, the adjuvant chemotherapy was adjusted to wPCb (carboplatin AUC = 2, d1 + paclitaxel 80 mg/m^2, d1, weekly).

To implement chemotherapy as early as possible after delivery, a cesarean section was performed at a gestational age of 37 weeks and 4 days in order to shorten the waiting time interval for delivery.

The postoperative pathological diagnosis showed a grade III IDC and no axillary lymph nodal metastases. The IHC results indicated ER(−), PR(−), HER2(−), and Ki67 (95%+).

No family history of breast cancer was reported in all the 3 cases. All of them were healthy, and ECOG scores were zero.

Case 2 patient experienced grade III bone marrow suppression once, white blood cell count was 1.9×10^9/L and neutrophil count was 0.64×10^9/L (Fig. 1). The granulocyte-colony stimulating factor (G-CSF) was administered to raise the white blood cell counts and neutrophil counts. No bone marrow suppression was observed in cases 1 and 3. No hematological toxicity, hepatic toxicity, and nephrotoxicity were observed in all the 3 cases.

The 1st ECG (electrocardiogram) result of case 3 showed occasional occurrence of ventricular premature beats, while the patient reported no complaint of discomfort. Therefore, no specific treatment was administered and no abnormality was observed in the ECG findings during the next 13 cycles of chemotherapy.

Uterine contraction appeared in all 3 patients. Uterine contraction was transient and ceased spontaneously in case 1, while caused preterm delivery in case 2. Case 3 patient

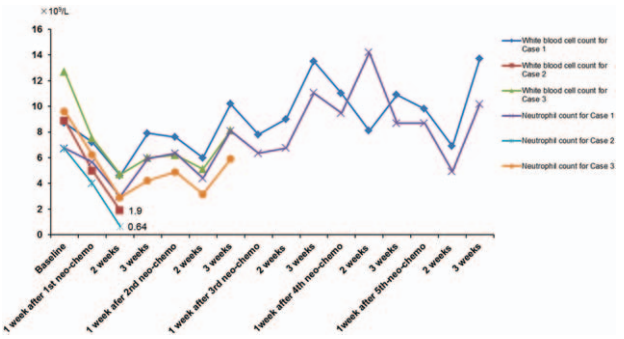

Figure 1. Variations of white blood cell and neutrophil counts in the 3 patients during pregnancy. Neo-chemo = neoadjuvant chemotherapy.

Table 3

Impact of chemotherapy on the fetus.

	Case 1	Case 2	Case 3
Cycles of intrauterine chemotherapy	5 cycles	1 cycle	2 cycles
Fetal movement during chemotherapy	Normal	Normal	Normal
Fetal heart beat during obstetric care	Normal	Normal	Normal
GA at delivery	39 wk	32 wk	37 wk and 4 d
Apgar score (points)			
1st minute	10	10	10
5th minute	10	10	10
Neonatal disease	No	Neonatal jaundice	No
Sex	Male	Female	Male
Height, cm			
Birth	51	40	49
2 mo	63.3	52	56
4 mo	68.5	59	67
6 mo	71.5	67	72
8 mo	75	70	75
12 mo	79.5	77	
18 mo	88		
Weight, kg			
Birth	3.83	2.3	2.89
2 mo	6.8	4.2	6.3
4 mo	8.4	6.3	8
6 mo	9.65	7.7	9.1
8 mo	11	9.2	10.4
12 mo	13	11.3	
18 mo	14.5		

Apgar Score is defined as rates a baby's appearance, pulse, responsiveness, muscle activity, and breathing with a number from 0 to 2 (2 being the strongest rating). The 5 numbers are then totaled. GA = gestational age.

experienced regular uterine contractions, which were stopped by using magnesium sulfate (7.5 g intravenously guttae, 1 day).

No patient experienced pregnancy-induced hypertension or eclampsia.

Adverse events included were nausea, hair loss, acid reflux, and constipation.

Till now, no recurrence or metastasis was observed in the 3 patients. The follow-up periods were 23-months for cases 1 and 2, and 13-months for case 3, respectively.

Neonatal jaundice occurred in the premature infant of case 2 (n = 1) who was recovered with phototherapy for 4 days and neonatal jaundice did not relapse after 1 month of follow-up. No malformation was observed in the 3 infants, and their heights and weights were all within the normal ranges to their corresponding gestational ages. All infants grew normally during the follow-up periods (Table 3). The time periods of sitting, standing, walking, and speaking of all the 3 infants were similar to that of normal infants. The infants had echocardiogram and ECG at the age of 2 years. Results showed that all outcomes were normal and LVEFs were 67% (case 1) and 63% (case 2), respectively. The infant of case 3 is under 2 years old till now.

3. Discussion

Currently, the well-recognized reasons for the poor prognosis of BCP include delay in diagnosis and postponement of treatment to assure birth of a healthy infant.[7] It is important to explore the suitable and effective treatment during pregnancy to achieve the win–win outcome for both patients as well as infants.

Chemotherapy during pregnancy is feasible and safe. First trimester is the main embryonic period and chemotherapy causes major congenital anomalies including neural-tube defects, amelia, atrial septal defect, ventricular septal defect, etc.[8] Second and early 3rd trimesters are the periods of central nervous system development and minor organ formation including ears, eyes, teeth, and external genitalia.[8] Distinct from the 1st trimester, the teratogenicity rate of chemotherapy during 2nd trimester and early 3rd trimester was similar to that of the normal pregnancy rate (3%).[9,10] Based on the current literature, no neurological damage such as cognitive impairment or hearing loss was observed during the long-term follow-up period.[11,12] Cardonick et al[11] investigated the central nervous system toxicity of chemotherapy-exposed children in utero and found that there was no statistical difference between the in utero chemotherapy-exposed children and nonexposed controls in the aspects of cognitive ability, cognitive scores, school performance, or behavioral competence. Therefore, we approved the feasibility and safety of chemotherapy during pregnancy. Also the 1st course of chemotherapy was given to all patients during 2nd and 3rd trimesters.

Anthracycline-based chemotherapeutic regimen followed by with or without taxanes was examined to be an optimal choice of treatment recommended by the ESMO clinical practice guidelines.[2] Amant et al[12] investigated the outcomes of infants when exposed in utero to chemotherapy, most of them are anthracycline-based, and found that their ECG and echocardiography were within the normal ranges. In our study, no complaints and clinical manifestations of heart discomfort were reported in children up to now. Moreover, the echocardiogram examination and ECG were normal. In 2010, studies showed that taxanes seldom crossed the placental barrier of pregnant baboons.[13,14] So, ESMO guidelines approved the safety of taxanes and recommended the use of taxanes during pregnancy if needed.[2] Cyclophosphamide passes through the placental barrier and enters into the breast milk; however, it is used during the 2nd and 3rd trimesters to reduce the teratogenicity rate from 18% during

the 1st trimester to 1%.[15] Based on the above studies, we had selected much safer chemotherapeutic drugs, including epirubicin (a kind of anthracyclines drugs) and paclitaxel (a kind of taxanes drugs), to conduct individualized treatment for the 3 patients in order to achieve the treatment effect and have healthy infants. Spontaneous delivery could occur any time after 34 weeks of gestation. Hence, ESMO guidelines suggested that chemotherapy should not be administered beyond 33 weeks of gestation and recommended that weekly paclitaxel regimen is preferred, to reduce the toxicity and adverse effects and avoid delivery during the nadir period.[2] Moreover, physiological increase in the number of white blood cells is observed in the pregnant women during the gestational period.[16] As a result, the bone marrow suppression was observed just once as a result of all 8 cycles. Considering the stage cT2N2M0 and no bone marrow suppression, case 3 was administered beyond 33rd week of gestation and underwent iatrogenic cesarean section in order to shorten the interval to receive follow-up treatment.

Adverse effects of chemotherapy during pregnancy are challenging to all patients, infants, and physicians. Cardonick et al[17] reported the gestational use of taxanes and found uterine contractions in 2 patients; while the side effects of neonates include premature birth, neutropenia, and hyperbilirubinemia. Our study results demonstrated uterine contraction in all the 3 patients during chemotherapy. Decision of drug inhibition or immediate delivery was made by the obstetricians according to the degree of contraction and the condition of fetus. Case 2 had preterm delivery, while the other 2 had transient uterine contraction, which was ceased spontaneously or by magnesium sulfate. The causes of preterm delivery are preterm premature rupture of membranes, lower genital tract and urinary tract infections, other pregnancy complications, uterine malformations, etc. Above all, though it is hard to say that chemotherapy is the direct cause of preterm delivery, we should pay attention to the uterine contractions during treatment. Our patients had acid reflux occasionally. However, since cimetidine and proton pump inhibitor are prohibited during pregnancy, oral administration of soda water was recommended by us for relieving the symptom.

4. Conclusion

The 3 cases discussed above have demonstrated feasibility and tolerance with the use of chemotherapy during the 2nd and 3rd trimesters. Our findings showed good efficacy with combined chemotherapeutic regimen of epirubicin and paclitaxel in the patients. Also, the findings demonstrated excellent fetomaternal tolerance with limited application of adjuvant drugs. Although our experience and conclusion were based on only 3 cases, this is the first Chinese report that covered the use of chemotherapy during pregnancy for BCP patients. More studies with larger sample size are required for further validation.

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