Taxane Use for Breast Cancer in Pregnancy: Neonatal Follow-Up Of Infants with Positive Detection of Intact Paclitaxel and Metabolites in Meconium at Birth

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Abstract

Paclitaxel is often excluded during pregnancy for women with breast cancer due to limited neonatal follow-up. We confirmed in utero fetal Paclitaxel exposure for 8 newborns. Birth details and follow-up to 36 months of age is reported. Meconium samples from newborns exposed to chemotherapy were screened by liquid chromatography-high resolution mass spectrometry while blinded to maternal treatment during pregnancy. Newborn information at birth and annually was obtained. Mean gestational age (GA) at cancer diagnosis and start of chemotherapy was 8.7 +/- 6.2 weeks and 17.1 +/- 3.5 weeks. Paclitaxel was started at a mean GA of 27.0 +/- 5.8 weeks. Paclitaxel followed Doxorubicin/Cyclophosphamide in 6 cases, 5-Fluouracil/Doxorubicin/Cyclophosphamide in 1, and was used alone in 1. Mean number of days between Paclitaxel and birth was 23 +/- 15. Identification of Paclitaxel and/or metabolites was made in all taxane exposed samples. Birthweight was < 10% for GA in 3 infants. Three anomalies occurred: hip dysplasia and mitral valve stenosis. The 3rd child was diagnosed with Cleidocranial Dysostosis, a familial anomaly. Mean age at pediatric follow-up is 18.7 +/- 9.3 months. Pediatricians report eczema and recurrent otitis media in 1 child, iron deficiency anemia and sinusitis in 2. One child is < 10% for height and weight at 15 months. All are meeting developmental milestones at median age of 18.7 months, range: 6–36 months. Conclusion: Up to 3 years of age, follow-up of neonates exposed to Paclitaxel in utero is reassuring. Continued observation of neonatal development is essential.

Introduction

Cancer diagnosis occurs in 1 in 1000 pregnancies [1]. The most common malignancies complicating pregnancy are breast cancer, Hodgkin’s and Non-Hodgkin’s lymphoma, and melanoma [1]. Approximately 1 in 5 breast cancers diagnosed in women aged 25 to 29 years is associated with a pregnancy, diagnosed either during pregnancy or during the first postpartum year. Given the recent trend for women to delay childbearing, we expect more cases of breast cancer to be diagnosed during pregnancy. The most common agents used during pregnancy include doxorubicin, cyclophosphamide, 5-fluouracil, and more recently paclitaxel. Neonatal outcomes after chemotherapy exposure during the second and third trimester have been reassuring with regards to malformations and general appearance at birth [2-9]. A limited number of studies provide longer follow-up including developmental and physical evaluation of chemotherapy-exposed children into the late teen years and young adulthood [7-9]. Given that the addition of taxanes to anthracycline-based (AC) regimens results in excellent response rates, longer time to progression, and improved outcomes for non pregnant women with breast cancer, offering taxanes to pregnant women could be preferred over an elective preterm birth to expedite starting taxanes postpartum. In fact, when evaluating the developmental outcomes of children exposed to chemotherapy in utero, preterm birth had a more significant impact on neonatal performance than chemotherapy exposure [8,9]. In a recent study, taxanes were demonstrated to be present in the meconium of exposed neonates, providing unequivocal evidence of in utero exposure [10]. Meconium, the first stool of a newborn that passes in the first few days after birth, begins to accumulate around the 13th week of
pregnancy, but is not excreted until birth, providing a unique window into gestational metabolism and exposures. In this study we provide follow-up on newborns positively screened to be exposed to paclitaxel in utero.

Materials And Methods

This study was approved by the Cooper Health System Institutional Research Board. Women diagnosed with cancer during pregnancy were offered enrollment in a multi center cohort study registered with clinicaltrials.gov NCT02749474 that collects diagnostic and treatment information as well as neonatal well being for this unique cohort of patients. Oncologists provided diagnostic and treatment details including the maternal body surface area (BSA), chemotherapeutic agent, doses, and dates of therapy during pregnancy. Neonatal birthweight, gestational age at delivery, and congenital anomalies were collected. Small for gestational age birthweight, defined as <10%, is documented using Fenton criteria for preterm infants or by World Health Organization (WHO) criteria for term infants. Major birth defects were defined according to the Metropolitan Atlanta Congenital Defects Program (MACDP) code modifications developed by the Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Public Health Service, U.S. Department of Health and Human Services, Atlanta, Georgia 30333. To evaluate fetal exposures, women were asked to provide newborn meconium on day one of life if they received chemotherapy during pregnancy. Additionally participants agreed to allow pediatric follow-up from pediatricians at 6 months and annually during the child’s birth month. Screening of the meconium using liquid chromatography-high resolution mass spectrometry (LC-HRMS) was previously described [10]. The newborns exposed to taxanes underwent inspection at birth, and then additional follow-up was requested from pediatricians at 6, 12, 24 and 36 months of age. Annual follow-up is ongoing.

Treatment regimens, dosing, maternal BSA, and timing of first treatment are detailed in Table 1. Mean gestational age at the first chemotherapy treatment 17.1 +/- 3.5 weeks and at the first taxane treatment 27 +/- 5.8 weeks. The mean number of days between last treatment during pregnancy and day of birth was 23 +/- 15 days. Meconium was provided for analysis with blinding with regards to the chemotherapy treatment given during pregnancy. For the 8 infants exposed to taxanes, with confirmed detected in meconium at birth, delivery details and neonatal follow-up are described in Table 2. Annual follow-up was requested from pediatricians including developmental age assessment, meeting of appropriate milestones, percentage for head circumference, height and weight, and the diagnosis of any medical disorders or anomalies diagnosed after birth.

Delivery and Birth Defects: Details of the quantification of paclitaxel and metabolites found in meconium has been previously described [10]. The mean gestational age at delivery was 36.6 ± 0.9 weeks, and mean birthweight 2530 ± 336g. Three term infants weighed less than the 10th percentile for their gestational age at birth per WHO criteria using gestational age and gender. Two children were noted to have a congenital anomaly at the time of birth. One child was born with a familial autosomal dominant anomaly identical to their affected parent; one child delivered breech was diagnosed with hip dysplasia, a
common association with malpresentation. While reviewing pediatric follow-up records, a third child was found to have congenital mitral stenosis during an echocardiogram at age 2 months performed due to the presence of a murmur. There was no significant difference in anomalies for 49 neonates exposed to taxanes in utero after completing anthracycline based chemotherapy compared to 58 exposed to this therapy without the addition of taxanes for breast cancer, p=0.29.

**Well being:** Median age at most recent pediatric evaluation is $18.7 \pm 9.3$ months. All children are meeting age appropriate milestones and none have been diagnosed with major medical disorders aside from typical childhood illnesses such as otitis media, eczema, anemia, and sinusitis.

**Discussion**

Recently, we have shown that paclitaxel crosses the human placenta as it was detected in the meconium of neonates exposed in utero [10]. Berveillier studies the transplacental transfer and placental accumulation of paclitaxel and docetaxel and found both were similarly low, especially in physiological conditions of albumin [11]. Studies in a non-human primate pregnant baboon model also demonstrated transplacental disposition of chemotherapeutics with fetal exposure to taxanes (paclitaxel and docetaxel) occurring hours after infusion [12]. Despite transplacental transfer of taxanes, several authors have documented reassuring fetal surveillance after in utero exposure to taxane chemotherapy [13-21]. Despite the detection of chemotherapeutics in human meconium, neonatal follow-up for these neonates is reassuring. A possible explanation for the low placental transfer of taxanes is the presence of transporters in the feto-placental unit which prevents the entry of xenobiotics. The most well known of these is the P-glycoprotein, or the MDR1 gene product which functions as an efflux pump that transports substrates away from the intracellular to the extracellular compartment, protecting the developing embryo and fetus from toxic substances [22]. P-glycoprotein has been detected in human placental trophoblasts from the first trimester to term [23]. In the mouse, inhibition of placental P-glycoprotein results in enhanced transplacental passage of digoxin, saquinavir, and paclitaxel into the fetus [24].

In all cases described here, paclitaxel and the other chemotherapy regimens were started after organogenesis was completed during the first trimester. All taxane-exposed children are meeting milestones with the longest follow-up to 3 years of age, and annual follow-up is ongoing.

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Tables

Table 1 Taxane Containing Chemotherapy Regimens During Pregnancy:
| Dose | Total | # of | GA DX | GA | Days | GA | T in | 3-OH T | 6-OH T |
|------|-------|------|-------|-----|------|-----|------|--------|--------|
| mg/m² | dose | Cycles | TX | Wks | Tx to | Wks | pg/mg | Pg/mg | Pg/mg mg |
| mg | Wks | Birth |
| + | 175 | 306 | | | 24.9 | 49 | 36.0 | 52.8 |
| | 1 | 2 | 13 | | 0 | 52.1 |
| T | 80 | 131 | 4 | 4 | 19 | 31.3 | 21 | 37.3 | 239.2 | 84.2 | 103.4 |
| | 80 | 138 | 12 | 2 | 18 | 18 | 40 | 34.7 | 446.3 | 100 | 136.3 |
| | 80 | 133 | | 23 | 23 | 37.3 |
| T | 12 | 8 | 13 | | | 865.2 | 117 | 131.8 |
| T | 80 | 140 | 6 | 15 | 17 | 30 | 15 | 37.0 | 431.2 | 97.5 | 106.4 |
| T | 80 | 164 | 3 | 15 | 21 | 33 | 3 | 36.4 | 367.5 | 88.9 | 86.8 |
| | 151 | | 22 | 25 | 36.7 | | | 231.4 | 213.6 |
| T | 80 | 12 | 6 | 14 | | | | 537.2 |
| T | 80 | 143 | 3 | 18 | 22 | 34 | 10 | 37.4 | 313.1 | 70.7 | 76.8 |

FAC 5Flouracil/ Doxorubicin/Cyclophosphamide
AC Doxorubicin/Cyclophosphamide
T Paclitaxel
GA Gestational Age
DX Diagnosis
TX Treatment
Wks Weeks

Table 2 Detection of Taxanes in Meconium Samples of Neonates Exposed to Chemotherapy in Utero: Neonatal Follow up: Delivery of Newborn, GA, birthweight and mean age at medical and developmental follow up
| GA (delivery) | Regimen | Birthweight (g) | Anomalies or Complications at Birth | Recent Age at Follow UP (months) | Meeting Developmental Milestones | Medical Concerns |
|---------------|---------|----------------|-----------------------------------|---------------------------------|--------------------------------|----------------|
| 37.4          | AC,T    | 3100           |                                   | 11.6                            | Yes                           | Iron deficiency anemia |
| 36.4          | AC,T    | 2200           | MV Stenosis age 2 months          | 24                              | Yes                           | Sinusitis |
| 37.0          | AC,T    | 2690           | IUGR                              | 19                              | Yes                           | <5% height and weight for age |
| 37.3          | AC,T    | 2200           | IUGR                              | 6                               | Yes                           | Eczema, otitis media |
| 34.7          | T       | 2200           | Parent and child have Cleidocranial Dysostosis-Autosomal Dominant | 15                              | Yes                           |                                  |
| 37.3          | AC,T    | 2495           | IUGR                              | 25                              | Yes                           |                                  |
| 36.0          | FAC,T   | 2863           |                                   | 10                              | Yes                           |                                  |
| 36.7          | AC,T    | 2495           | Hip Dysplasia, breech             | 24                              | Yes                           |                                  |

GA Gestational Age
IUGR Intrauterine Growth Restriction
MV Mitral Valve

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