Fetal Renal Insufficiency Following Trastuzumab Treatment for Breast Cancer in Pregnancy: Case Report und Review of the Current Literature

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Keywords

Fetus · Renal insufficiency · Trastuzumab · Breast cancer · Pregnancy

Summary

Some drugs are known for their fetal nephrotoxicity and should be avoided during pregnancy. We report on a pregnant woman suffering from breast cancer who received a weekly neoadjuvant trastuzumab (Herceptin®) therapy from 15 weeks of gestation onward, in addition to a 3-weekly carboplatin/docetaxel chemotherapy. Fetal renal insufficiency with anhydramnios and missing visualization of the fetal bladder developed at 21 weeks. After discontinuation of trastuzumab and repeated instillation of amniotic fluid, the amount of amniotic fluid remained stable after 24 weeks of gestation. After caesarean section at 34 weeks because of fetal growth restriction, the renal function of the neonate was normal postnatally. In accordance with the current literature, our case shows a reversible adverse effect of trastuzumab on the fetal renal function and confirms the current recommendation that trastuzumab in pregnancy should be avoided. In pregnancies exposed to trastuzumab, treatment should be discontinued and the fetus should be closely monitored, with particular attention to the amniotic fluid and the fetal bladder volume, as these reflect fetal renal function.

Schlüsselwörter

Fetus · Niereninsuffizienz · Trastuzumab · Brustkrebs · Schwangerschaft

Zusammenfassung

Für einige Medikamente sind fötale, nephrotoxische Nebenwirkungen bekannt, weshalb eine Therapie mit diesen Medikamenten während einer Schwangerschaft vermieden werden sollte. Wir berichten von einer Schwangeren mit Brustkrebs, die neoadjuvant ab der 15. Schwangerschaftswoche (SSW) zusätzlich zur 3-wöchentlichen Carboplatin/Doxetaxel-Chemotherapie wöchentlich Trastuzumab (Herceptin®) erhalten hatte. Ab der 21. SSW zeigte sich ein Anhydramnion als Zeichen einer fötalen Niereninsuffizienz. Eine fötale Harnblasenfüllung war nicht darstellbar. Nach sofortigem Absetzen von Trastuzumab und wiederholter wöchentlicher Fruchtwasserauffüllung normalisierte sich die Fruchtwassermenge dann ab der 24. SSW und blieb im Verlauf normal. Im weiteren Verlauf der Schwangerschaft entwickelte sich eine fötale Wachstumsretardierung, die zur Entbindung durch Sectio caesarea in der 34. SSW führte. Die weitere postnatale Entwicklung sowie die Nierenfunktion des Neonaten waren unauffällig. In Übereinstimmung mit bisherigen Publikationen zeigt unser Fall eine Trastuzumab-bedingte, reversible fötale Niereninsuffizienz und bestätigt somit aktuelle Empfehlungen, eine Therapie mit Trastuzumab in der Schwangerschaft zu vermeiden. Nach erfolgter Gabe in der Schwangerschaft sollte Trastuzumab sofort abgesetzt und die weitere Schwangerschaft engmaschig kontrolliert werden, wobei besonderes Augenmerk auf die Fruchtwassermenge und die fötale Harnblasenfüllung gelegt werden sollte, da diese die adäquate fötale Nierenfunktion widerspiegeln.

Introduction

Breast cancer in pregnant women is rare, with an incidence of 1 in 3000 live births [1–3]. But with increasingly higher maternal age at time of conception the incidence of malignant diseases in pregnancy is rising. Thus, we are more frequently confronted with the question of compatibility of chemotherapy and pregnancy, and information about possible side effects on the fetus is of increasing clinical relevance [4–12]. The recent literature describes new therapeutic options for breast cancer during pregnancy and proves the feasibility and tolerability of, e.g., anthracycline- or taxane-containing regimens without compromising the fetus [3, 6, 7, 9–35], especially if chemotherapy is administered during the second or third trimester [6, 7, 10–12, 16, 17, 23–25, 36–38].

Case Report

A 38-year-old pregnant woman at 11 + 6 weeks of gestation was diagnosed with an estrogen receptor (ER)/progesterone receptor (PR)-positive, HER2-overexpressing invasive ductal carcinoma of the breast with ductal carcinoma in situ, without further signs of metastatic disease. According to the patient's request, breast-conserving surgery and axillary lymph node dissection were postponed until after delivery. Instead, the decision for neoadjuvant chemotherapy with 3-weekly docetaxel (75 mg/m²) and carboplatin (area under the curve (AUC) 6) (q21d) in addition to weekly trastuzumab (Herceptin®, 4 mg/kg) (Breast Cancer International Research Group (BCIRG)006) was made by the attending, non-local physician, and the first and second cycles of taxotere, carboplatin, Herceptin (TCH) were administered at 14 + 6 and 17 + 6 weeks of gestation, respectively, until the patient was referred to our department at 20 + 4 weeks of gestation with anhydramnios and failure to visualize the fetal bladder. As fetal renal insufficiency was suspected, we discontinued trastuzumab therapy immediately and performed weekly instillations of amniotic fluid, as the normal amount of amniotic fluid is crucial for fetal lung maturation and development. After 3 instillations, the amount of amniotic fluid remained stable after 24 weeks of gestation. Simultaneously, neoadjuvant chemotherapy was continued externally again, with docetaxel and carboplatin at 21 + 0, 24 + 0, 27 + 0 and 30 + 0 weeks of gestation. At 28 weeks of gestation, fetal growth restriction was diagnosed with normal amniotic fluid volume and normal fetal Doppler flow parameters. As the growth restriction worsened, a caesarean section was performed at 33 + 2 weeks and a dystrophic premature male neonate was born (birth weight < 3rd percentile). The neonatal period was characterized by inconspicuous neonatal development and normal renal function with normal urinalysis. 13 days post partum, the mother underwent lumpectomy and sentinel lymph node dissection of 2 tumor-free lymph nodes.

Discussion

Chemotherapy during the first trimester of pregnancy – the time of fetal organogenesis – is associated with an increased incidence of teratogenicity and an increased rate of fetal malformation compared with administration in the second or third trimester [26, 38–42]. Earlier reports with an association of chemotherapy and fetal growth restriction [26, 38–42] could not be confirmed in the recent literature [10, 12, 17, 36].

Whether the growth restriction leading to preterm delivery of a dystrophic neonate in our case was caused by the chemotherapeutic drugs, by trastuzumab or neither of them remains unclear. As Doppler sonography failed to demonstrate any sign of uteroplacental dysfunction, it is most likely drug induced.

If chemotherapy during pregnancy is unavoidable, some chemotherapeutic drugs are considered safer than others and should be used preferably: Contraindicated in pregnancy are the folic acid antagonist methotrexate or aminopterin [43–49], and thus the previously most common adjuvant regimen cyclophosphamide/methotrexate/fluorouracil (CMF) [7]. Other drugs, like the pyrimidine-antagonist 5-fluorouracil, should be avoided during pregnancy because of limited experience in pregnancy [10, 11, 16, 17, 49]. For other drugs, reports are contradictory, e.g. reports on the effect of cyclophosphamide [7, 10, 24, 37, 38, 43, 50, 51]. Until now, the best body of evidence exists for anthracyclines, mostly because these drugs have also been used for a long time in young women with hematological malignancies [7, 10, 11, 25, 27, 28, 38, 52–58].

In our case, the pregnant woman was exposed to a neoadjuvant docetaxel/carboplatin/trastuzumab regimen. A significant transplacental transfer of platinum-containing drugs like cis- and carboplatin was reported in previous studies from the second trimester of pregnancy onward, but no fetotoxic effect was seen in any of the published cases [51, 29–31, 59–60]. Thus, administration of carboplatin during pregnancy seems to be reasonable and the benefits from its use in pregnancy may be acceptable despite a possible risk for the fetus.

The anti-neoplastic effect of taxanes is based on the inhibition of the synthesis of microtubules. Experience with fetal exposition to taxanes shows no adverse effect on the fetus, and exclusively healthy babies were born [18–23, 26, 30, 31, 33, 34, 61].

Trastuzumab (Herceptin®, Roche Pharma AG, Grenzach-Whylen, Germany) is a monoclonal IgG1 antibody to the human epidermal growth factor receptor HER2. The transplacental transfer of IgG1 antibodies is documented [62] and has been shown for other IgG1 antibodies like rituximab [63] and infliximab [64]. As HER2 is also expressed in embryofetal tissue, it may be critical for fetal development. Now sufficient reports on trastuzumab-therapy in pregnancy have been published in which serious adverse effects on fetal development were documented to show that trastuzumab in pregnancy is contraindicated [3, 10, 13, 15–17, 32, 35, 65–73]. Most cases report on fetal nephrotoxicity with renal insufficiency with oligo- and anhydramnios [32, 35, 65, 66, 72], but with spontaneous improvement of renal function after discontinuation of trastuzumab. Another case of trastuzumab in pregnancy showed oligohydramnios and vaginal bleeding at 27 weeks of gestation. A caesarean section was performed subsequently for ongoing bleeding. The preterm infant developed respiratory failure, capillary leak syndrome, persistent infections, and necrotizing enterocolitis and ultimately died [71].

Three other case reports showed uneventful pregnancies without fetal impairment and with normal fetal growth. Each pregnancy resulted in the birth of a healthy baby [67–69]. Another case described a pregnancy exposed to trastuzumab until 24 weeks of gestation. Therapy was then discontinued because of asymptomatic persistent mildly reduced ejection fraction. The pregnancy was otherwise uneventful. A healthy baby was born at 37 weeks of gestation by caesarean section due to breech presentation. No data on fetal renal function were available [70].

Conclusions

In accordance with the current literature, our case showed a trastuzumab-induced transient fetal renal insufficiency with

anhydramnios, with improvement of amniotic fluid volume and complete remission of renal function after discontinuation of trastuzumab. Although HER2 overexpression is a negative marker for maternal prognosis [74, 75] and a combination of chemotherapy with trastuzumab significantly improves maternal survival, therapy in pregnancy should be avoided. If accidentally exposed to trastuzumab, treatment should be discontinued immediately and the fetus should be closely monitored with particular attention to the amniotic fluid and the fetal bladder volume as these reflect fetal renal function.

Disclosure Statement

All authors have no financial or personal conflicts of interest.

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