Trastuzumab in pregnancy associated with poor fetal outcome

Trastuzumab (Herceptin®), an mAb targeting the epidermal growth factor receptor HER2, is used as standard of care in patients with HER2-overexpressing tumors. A relevant number of younger women with childbearing potential are being treated with this immunoglobulin (IgG1) antibody. We report a patient with metastatic breast cancer who was treated with trastuzumab during pregnancy. The baby was born preterm and developed a severe respiratory distress and capillary leak syndrome with fatal outcome.

The patient was diagnosed at the age of 29 with a 3-cm left breast mass. A biopsy showed an infiltrating ductal–lobular carcinoma, estrogen receptor positive and progesterone receptor negative. HER2 overexpression (3+ DAKO score), G2. In a clinical trial, neo-adjuvant chemotherapy with three cycles of epirubicin 150 mg/m² every 2 weeks, followed by three cycles of paclitaxel 250 mg/m² every 2 weeks, was applied. In the surgical specimen, no remaining tumor was found (ypT0 ypN0). The patient received three cycles of combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil after surgery followed by endocrine treatment with tamoxifen. She presented 1.5 years later with pulmonary metastases. After 24 administrations of vinorelbine (Navelbine®) 25 mg/m² and trastuzumab 2 mg/kg weekly, she developed a complete remission. Therapy with trastuzumab was continued with 6 mg/kg every 3 weeks. Seven months after cessation of vinorelbine, the patient reported to be pregnant. According to fetal growth development, the patient was in the 23rd week of gestation. Detailed anatomical ultrasound scan showed no abnormalities. To evaluate the patient’s prognosis, a magnetic resonance scan was carried out which showed two
cerebral metastases and radiation of the brain was planned. After detailed counseling including her prognosis, the patient decided to continue pregnancy.

Four weeks after diagnosis of pregnancy, the patient presented with oligohydramnion and vaginal bleeding. Fetal lung maturation was induced with corticosteroids. One week later, a caesarean section had to be carried out due to strong vaginal bleeding although no abrasion of the placenta could be diagnosed. The female newborn infant weighed 1015 g (57th percentile for 27 weeks of gestation), pH value of the umbilical artery was 7.48 and APGAR score 8/7/6. The placenta showed no abnormalities by histological examination. The newborn infant developed respiratory failure necessitating mechanical ventilation, uncommonly strong capillary leak syndrome, persisting infections and necrotizing enterocolitis. The baby died due to multiple organ failure 21 weeks after delivery.

As HER2 is expressed in embryofetal tissue, it might be critical to fetal development. In murine knockout studies, deletion of the HER2 gene was fatal to embryos at early gestation due to cardiac and neural dysfunction. Trastuzumab has been assigned as a category B pregnancy risk on the basis of trials in monkeys which showed no apparent fetal harm [1]. The possibility of fetal damage when an antibody to HER2 is administered has not been excluded.

To our knowledge, information on fetal outcome after trastuzumab exposure in utero is limited to five case reports. Watson [2] reported anhydramnion associated with trastuzumab application until 23 weeks of pregnancy which was reversible after withdrawal of the drug. Labor was induced at 37 weeks, and the baby had normal renal function after delivery and developed well. Fanale and co-workers [3] reported persistent oligohydramnios during treatment with trastuzumab and vinorelbine at weekly intervals until induction of labor at 35 weeks’ gestation. Waterston and Graham [4] reported a normal pregnancy that resulted in a normal vaginal delivery of a healthy baby after exposure to trastuzumab. The patient had received two cycles of trastuzumab before she became pregnant. Trastuzumab therapy was discontinued. Bader et al. [5] reported a patient who presented with metastatic breast cancer and was 17 weeks pregnant. At 26 weeks’ gestation, a combination of paclitaxel and trastuzumab every 3 weeks was induced. After two cycles of therapy, the amniotic fluid had reduced to almost anhydramnion and fetal growth had stopped. After lung maturation, a caesarean section was carried out at 32 weeks’ gestation. The preterm born (10th percentile) showed signs of bacterial sepsis with hypotension, renal and respiratory failure. The further development was normal. Shrim et al. [6] presented a patient with metastatic breast cancer who was treated with trastuzumab during the first 24 weeks of pregnancy. A caesarean section was conducted at 37 weeks and resulted in a healthy baby.

Our patient received 25 cycles of trastuzumab (6 mg/m² every 3 weeks) before she became pregnant. After eight more cycles, she reported to be pregnant. After one more cycle, the caesarean section was carried out. To our knowledge, this is the highest dose of trastuzumab applied to a pregnant woman that has been reported (56 mg/kg total dose). We report reduction of amniotic fluid during treatment with trastuzumab in pregnancy which has also been reported in other studies. Apart from the problems due to prematurity, the newborn showed an unexpected strong capillary leak syndrome and respiratory insufficiency.

In conclusion, this case may indicate that trastuzumab in higher doses affects fetal development and results in an impaired prognosis of the newborn despite the reassuring findings in other case reports. In the context of the increasing number of patients treated with this drug including the adjuvant setting, this is of increasing clinical relevance.

I. D. Witzel1*, V. Mueller1, E. Harps2, F. Jaenicke1 & M. deWit3

Departments of, 1Gynecology, 1Pediatrics, University Hospital Hamburg, Hamburg, 2Department of Haematology and Oncology, Vivantes Klinikum Neukoelln, Germany

(*E-mail: iwitzel@uke.uni-hamburg.de)

references


doi:10.1093/annonc/mdm542