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Pregnancy on vandetanib in metastatic medullary thyroid carcinoma associated with multiple endocrine neoplasia type 2B

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To the Editor

Vandetanib is a tyrosine kinase inhibitor (TKI) used in the treatment of medullary thyroid carcinoma occurring in >95% of patients with multiple endocrine neoplasia type 2b (MEN 2b). Pregnancy in women with MEN 2b on vandetanib is previously unreported and has multiple potential implications for both the mother and developing fetus [1].

We describe the case of a 22 year old woman with a background of MEN 2b who was first diagnosed aged 6 presenting with marfanoid habitus, and oral mucosal neuromas. Screening of mutations in the RET gene revealed a missense mutation (M918T/N) and histology from her resulting thyroidectomy confirmed medullary thyroid carcinoma with vascular invasion. She had four further resections for residual disease in lymph nodes and had lung metastases. Aged 16, she commenced on vandetanib 125mg once daily (100mg/m²), for disease progression (calcitonin 24950 ng/l, normal range <4.8) (Figure 1).

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The risk of pregnancy including: the potential implications of vandetanib on a developing fetus, the physiological strain with metastatic medullary thyroid carcinoma, risk of progression off vandetanib treatment, uncertain life expectancy, the risk of inheritance of MEN2b, her low body weight (BMI 15.9kg/m²), reduced gas transfer on lung function with desaturation on shuttle walk and potential risk of pheochromocytoma, were extensively discussed. Despite this counselling and having been on the oral contraceptive pill, she had an unplanned natural conception detected prior to a planned CT. She immediately discontinued her vandetanib, at around 6 week's gestation. Her preconception calcitonin was 6040 ng/l and carcino-embryonic antigen (CEA) 57.9 µg/l (<3.5). After counselling she continued the pregnancy and opted for postnatal RET gene testing of cord blood.

At the time of her positive pregnancy test, her TSH was 47mu/l (0.35–4.5) and her free T₄ was 14.2 pmol/l (11.0–24.0), having previously been normal. Her thyroxine was increased from 125mcg to 175mcg once daily (and 200mcg at 28 weeks pregnant). Her TSH remained above the reference range throughout pregnancy (with intermittently high FT₄ and previously recognised problems with compliance). Plasma metanephrines remained normal and blood pressure low in pregnancy. Fetal growth and amniotic fluid volume were normal on ultrasound at 20, 28 and 32 weeks.

At 34+2 weeks, she presented spontaneously in labour with a breech presentation leading to an emergency caesarean section (female infant, birth weight 1.99 kg (25th centile), requiring 30 seconds of inflation breaths then spontaneously ventilating with an APGAR of 7 at 1 minute). The infant had 48 hours of antibiotics and dextrose (blood glucose 2.7mmol/l). Cord blood analysis showed no RET mutation. A soft systolic murmur with normal echocardiogram was felt to be a normal childhood variant. There were no skeletal malformations or soft tissue abnormalities and at nine months the infant has met all her milestones.

Nine months postnatally the patient has shown some progression of tumour markers (Calcitonin 15860ng/l, CEA 84.8ug/l), but her anatomical disease is stable and she remains off vandetanib.

This is the first reported case of a pregnancy with MEN2b whilst on vandetanib and with a favourable outcome. Data from the use of other TKIs in pregnancy (predominantly imatinib in chronic myeloid leukaemia) shows 10–20% of maternal exposure during the 1st trimester to TKIs results in fetal problems or spontaneous abortion[2]. The fetal problems of skeletal malformations, soft tissue abnormalities and small for date observed in babies exposed to TKIs in-utero were consistent with the observations from studies of vandetanib in rats[3]. No data for the transplacental transfer of vandetanib exists but observations from the use of other TKIs show placental transfer occurs [4]. Literature from the use of other TKIs in CML recommend that drugs must be avoided during organogenesis, weeks 5–13, however there were no major consequences in this patient[2].

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Figure 1.

A timeline of events for our patient including calcitonin levels at key points.