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CHAPTER 8

Severe adverse reaction to vemurafenib in a pregnant woman with metastatic melanoma

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ABSTRACT

Targeted therapies have drastically changed the management of metastatic melanoma and have shown encouraging results on tumour progression but are also known for their high rates of adverse reactions. In general, targeted therapies are contraindicated during pregnancy due to concerns about teratogenesis. For the BRAF V600 inhibitor vemurafenib, the available literature about the effects on human pregnancy is limited to a single case report. In patients with metastatic melanoma that wish to continue their pregnancy, targeted therapies like vemurafenib offer the only possibility of improving maternal outcome. In this article, we report on a pregnant woman with metastatic melanoma who was treated with vemurafenib during pregnancy and experienced a fatal adverse reaction.

INTRODUCTION

Management of metastatic melanoma has changed drastically in the last 5 years due to the introduction of immunotherapy and targeted therapies following the poor response to chemo- and radiotherapy.[1] These new treatment options have shown encouraging results in patients with metastatic melanoma but can also cause severe side effects.[1,2] These side effects range from skin rash to fatal toxic reactions.[3,4]

Due to concerns about teratogenic effects, the use of targeted therapies in pregnant women with metastatic melanoma is considered contraindicated. Concerns about teratogenesis are based on data from pregnant monkey models, where targeted therapy agents crossed the placenta and caused increased rates of miscarriages, stillbirths, premature births, neonatal deaths, and urogenital tract malformations.[5] Little is known about the effects of the BRAF V600 inhibitor vemurafenib during pregnancy, which has only been re-ported in a single case report.[6] In the pregnancy described in this case report, the authors observed marked fetal growth restriction, necessitating an emergency caesarean section at a gestational age of 30 weeks due to fetal distress. No congenital malformations were observed.[6]

Here, we present the second report of vemurafenib during pregnancy, describing a poor obstetric outcome and severe maternal side effects. We describe a patient who developed metastatic melanoma during a twin pregnancy and developed a fatal toxic reaction to treatment with vemurafenib.

CASE REPORT

Our patient was a 30-year-old woman who was diagnosed with stage III (T4bN1a) superficial spreading melanoma of the hollow of the right knee in 2009. She was treated with excision and underwent lymphadenectomy. No other adjuvant treatment was initiated. In 2015, she was diagnosed twice with a solitary “in-transit” metastasis on the right leg for which excision was performed. At the end of 2015, a third solitary in-transit metastasis on the right leg was diagnosed, which was also excised, unfortunately without achieving histological radicality. Due to the persistent recurrences of metastatic disease, BRAF mutation was analysed and showed BRAF V600 positivity of the tumour. At that time, ultrasound showed a viable, intrauterine monochorionic-diamniotic twin pregnancy with a gestational age of $6^{5/7}$ weeks. Intralesional chemotherapy was indicated due to the non-radical excision, but was deemed unsafe considering the early pregnancy. Instead, re-excision under local field block anaesthetic was performed. One month later, another two in-transit metastases on the right leg were excised.

Two months after the last excision, she presented to the emergency room with abdominal pain, persistent vomiting, and constipation. Ultrasound and MRI showed an intussusception of the jejunum over a length of 10–15 cm, para-aortal lymphadenopathy, and a viable pregnancy of 18 weeks. She underwent a laparotomy, confirming the diagnosis of intussusception. The affected jejunum was resected. Histologic examination of the resected bowel and a sample of the tumours palpable in the mesentery showed metastatic melanoma. A PET/CT scan at $21^{6/7}$ weeks of gestation (low-dose ^{18}F-FDG, with bladder catheter) showed multiple cutaneous and breast metastases. An MRI of the brain showed solitary metastases in the temporal lobe. Due to the high tumour load, non-viable gestational age with the wish to continue her pregnancy and a BRAF V600 pathogenic mutation of the tumour, the patient was started on vemurafenib (twice a day, 960 mg) at a gestational age of $22^{5/7}$ weeks after extensive counselling. At that time, both fetuses had normal weight on ultra-sound, and no congenital anomalies were seen. Twelve days after commencing vemurafenib, our patient reported some mild skin toxicity, starting with some erythema on the face and back. The skin lesions rapidly worsened within 9 days with profound erythema and blisters on the neck, thorax, and arms covering over 70% of her body surface area, and purulent discharge from the eyes. Following this rapid progression of skin toxicity, our patient was admitted to the hospital and vemurafenib was immediately discontinued. Skin biopsy showed toxic epidermal necrolysis (TEN).

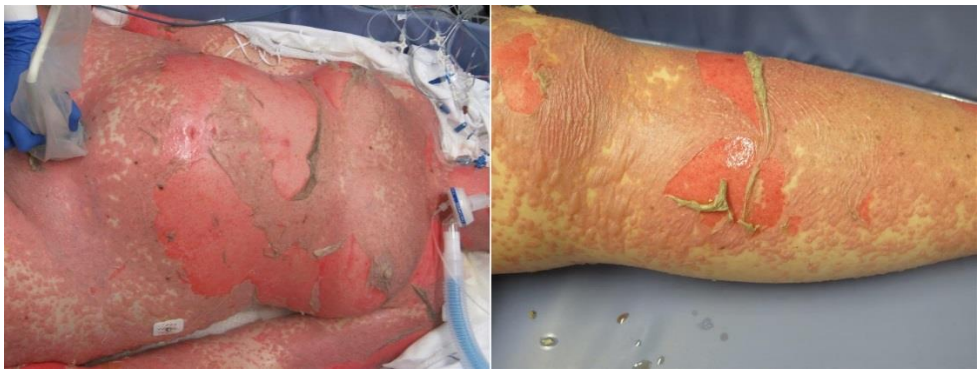

Figure 1. Skin lesions 25 days after start vemurafenib.

The patient was admitted to the intensive care unit the next day, where she was sedated and intubated for pain management. She required extensive rehydration due to significant insensible loss. In addition, betamethasone for fetal lung maturation was given in anticipation of preterm delivery because of maternal deterioration. There were no signs of

spontaneous preterm labour or intrauterine infection. At a gestational age of $26^{2/7}$ weeks, 25 days after the start of vemurafenib and within 1 day after intubation, the patient was transferred in a sedated state to an academic centre with both a neonatal intensive care unit (NICU) and burn specialty unit to provide optimal care for her second-degree TEN lesions, which now covered 98% of her body and oral mucosa (Fig. 1). On arrival, she was found to be in labour and she delivered both children while still sedated (first baby by forceps extraction, second baby by breech extraction). Two baby boys were born with birth weights within the normal range; one with a birth weight of 950 g and an APGAR score of 2 and 3 at respectively 5 and 10 min and one with a birth weight of 900 g and an APGAR score of 6 at 5 and 10 min. Both children were admitted to the NICU.

During the burn centre hospitalization, some re-epithelialization occurred, but unfortunately, the patient suffered several episodes of wound infection which delayed the wound healing. Initial topical treatment with alginate dressing was replaced by silver sulphadiazine upon diagnosis of pseudomonas wound infection. The mucosal lesions in the mouth caused significant bleeding. Oral rinsing with povidone solutions seemed effective but caused a iodide intoxication with hypothyroidism and a high anion gap acidosis. Corneal erosions and conjunctival adhesions were treated intensively in collaboration with the ophthalmologist. The first weeks were characterized by fluid loss and oedema, and pleural effusion complicated weaning from the ventilator. Once stabilized, the patient responded well to diuretics. Renal function remained normal throughout the burn centre stay. After delivery, oncological treatment with pembrolizumab would have been indicated once the TEN had improved and clinical condition improved. However, 53 days after delivery and 78 days after the start of vemurafenib, and before our patient could start with pembrolizumab, she died of an intra-cranial haemorrhage due to metastatic disease.

Both children were discharged from NICU to special nursery care 59 days after delivery and were discharged home 95 days after delivery. At a corrected age of 15 months, physical examination showed no abnormalities. Mental development was assessed using the Bayley Scales of Infant and Toddler Development (BSID). The first-born boy (birth weight 950 g) is developing normally, with a Bayley cognitive development score of 82 (developmental age of 15 months). The second boy (birth weight 900 g) was not able to undergo cognitive testing due to persisted crying, but his family did not notice any developmental delay. Long-term follow-up is needed to evaluate their long-term neurodevelopment.

DISCUSSION

In this case report, we presented a patient with metastasized melanoma with a BRAF mutation. Treatment with vemurafenib led to severe toxic epidermal necrolysis. This is the second published case report of treatment with vemurafenib for metastatic melanoma during pregnancy and the first to report no direct adverse effect on the fetus, but severe maternal side effects resulting in spontaneous early preterm delivery of twins and maternal death. The incidence of cancer complicating pregnancy is approximately 1 in 1000 pregnancies, and tumour types diagnosed during pregnancy do not differ from non-pregnant premenopausal women.[7] Six percent of all cancers diagnosed during pregnancy are melanomas, making it the fifth most common cancer in pregnancy.[8] In the overall population, including premenopausal women, the incidence of melanoma has been rising.[9,10] This, in combination with increasing age during pregnancy and the consequent increase in the risk of cancer during pregnancy, makes the problem of melanoma during pregnancy very relevant.[11,12]

With the introduction of novel targeted oncological therapies with encouraging results, the use of these therapies during pregnancy will become increasingly relevant. Previous studies on the effect of chemotherapy during pregnancy have shown that chemotherapy after the first trimester is likely to have limited long-term ill effects on the development of the exposed offspring, while prematurity negatively impacts developmental offspring out-comes.[13] Encouraged by these findings, chemotherapy is increasingly being applied during pregnancy without inducing preterm delivery prior to treatment. However, in cases where conventional chemotherapeutic options cannot improve prognosis, pregnant women may increasingly consider novel targeted cancer therapy, of which little is known about fetal and maternal side effects.

Even though this case did not show any direct negative impact on either of the children, the severe toxic reaction in the mother likely contributed to the spontaneous early preterm delivery, aggravating the adverse indirect effects on the neonatal and possibly the long-term paediatric outcome. Unfortunately, in this particular case, the use of vemurafenib did not seem to improve maternal outcome either.

Various adverse reactions to vemurafenib are common but range from mild skin rash (in over 90% of patients) to severe dermatotoxic, hepatotoxic and renal toxic effects (<1%).[3,4] Toxic epidermal necrolysis has been described in less than 1% of the patients using vemurafenib. Discontinuation of treatment with vemurafenib is imperative for curation. It is unclear whether the described toxic reaction in our patient was influenced by the pregnancy-related changes in pharmacokinetics. These altered pharmacokinetics are caused by (1) expansion of plasma volume leading to dilution of plasma proteins and

decreased concentration of drugs, (2) enhanced renal excretion of medication secreted by the kidneys, (3) altered liver metabolism changing the concentration of drugs metabolised by the liver, and finally (4) delayed absorption of oral medication from the stomach due to slower gastric motility.[14]

Vemurafenib is a serine-threonine kinase inhibitor and a substrate of the drug-metabolizing enzyme cytochrome P450-3A4 (CYP3A4). Over 99% of vemurafenib is bound to human albumin and α1-acid glycoprotein and it is mainly eliminated by hepatic clearance (94%).[15] Plasma concentrations of proteins, including albumin and α1-acid glycoprotein, decrease by up to 20–40% at term in pregnant women and can lead to a significantly increased proportion of unbound (active) vemurafenib.[14] Renal vemurafenib clearance is only 1%; therefore increased renal excretion is unlikely to offset increases in active plasma vemurafenib. Hepatic clearance of vemurafenib is only partially mediated by CYP3A4.[15] Increased oestradiol in pregnant women upregulates CYP3A4 leading to an increased hepatic metabolism and clearance of vemurafenib.[14] Since only part of the excretion of vemurafenib is CYP3A4 mediated, it is possible that this does not compensate for the increased unbound fraction of medication due to decreased plasma proteins. The balance between dilution on the one hand and decreased metabolism and excretion on the other hand is un-known because exact concentrations of vemurafenib in plasma have not been measured in pregnant patients. Changed pharmacokinetics could therefore theoretically lead to more (severe) adverse reactions during pregnancy.

In conclusion, targeted therapies like vemurafenib during pregnancy must still be considered experimental: the range of possible side effects on pregnancy as well as the effects of pregnancy on the incidence and severity of side effects is largely unknown. Our case adds that, beside possible effects on fetal growth, vemurafenib-induced skin toxicity may be exacerbated by pregnancy. Management of pregnant patients with cancer, in which an experimental treatment is deemed necessary, must be conducted by an experienced multidisciplinary team to provide the patient and her family with the best possible information and care. International registration studies of the rare cases of cancer in pregnancy and its management as performed by the International Network on Cancer, Infertility and Pregnancy (INCIP), www.cancerinpregnancy.org, are the only method forward in acquiring the necessary knowledge on this niche topic.

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