

## Treatment of Metastatic Malignant Melanoma With Vemurafenib During Pregnancy

### Introduction

The prognosis of stage IV malignant melanoma (MM) has for decades remained poor with median survival of 6 to 9 months.<sup>1</sup> Half of MM tumors carry an activating mutation of the proto-oncogene, B-RAF. The BRAF-inhibitor vemurafenib increases overall and progression-free survival compared with treatment with the chemotherapeutic agent dacarbazine in MM patients with advanced disease.<sup>2</sup> Vemurafenib is since August 2011 approved by the US Food and Drug Administration and since January 2012 by the European Medical Agency.

Treatment strategies in pregnant patients suffering from cancer require multidisciplinary approaches.<sup>3</sup> To our knowledge, this is the first described case of therapy with the BRAF inhibitor vemurafenib during pregnancy. MM is a common disease, its incidence grows rapidly and vemurafenib is becoming an established treatment. In addition, MM occurs frequently in younger people and the B-RAF mutation is more common in younger patients. These factors mean that similar cases are highly likely to occur in the future making this report of particular value.

### Case Report

We present the case of a 37-year-old Swedish woman who suffered from generalized MM and who was treated with vemurafenib during pregnancy. After primary excision by the general practitioner of a 3.6-mm ulcerated melanoma located in the left hypochondriac region, the patient was operated on in January 2010 at the regional hospital of Falun. Wide excision and removal of the sentinel node that was negative for cancer cells were carried out. In April 2011, a subcutaneous metastasis over the thoracic spine was removed. However, [<sup>18</sup>F]fluorodeoxyglucose-positron emission tomography and computed tomography scans did not reveal any further metastases. Four months later, lesions reoccurred locally at both excision sites, and were subsequently removed. At that time the patient was already at the end of the first trimester of pregnancy. Both the patient and her husband were aware of the high risk for developing incurable metastatic MM during pregnancy but were determined to carry on with the pregnancy. In November 2011, ultrasound was indicated due to right flank pain and elevated transaminases, revealing multiple liver lesions. Biopsy confirmed the melanoma nature of these lesions.

The patient was referred to Uppsala University Hospital (Uppsala, Sweden) because she was suffering from metastatic disease and in the 22nd week of pregnancy. According to the legislation of the Swedish National Board of Health, abortion cannot be considered as an option after that week. Further investigation with magnetic resonance imaging revealed metastatic disease including the lungs, but no metastases or lesions in the fetus or placenta. Since BRAF mutation in

codon V600 was identified, the patient was considered as a candidate for treatment with vemurafenib.

After multidisciplinary discussions between the patient and specialists in Oncology, Obstetrics, and Neonatology, it was decided for the benefit of both the patient and the fetus that treatment with vemurafenib should be initiated immediately and not postpartum. After approval by the Medical Products Agency, treatment with vemurafenib at the standard dose of 960 mg twice daily was started at week 25 after the patient had received corticosteroids to advance the normal lung development of the fetus.

At the time of the initiation of the treatment the patient had already developed a new subcutaneous metastasis in the back. The patient responded to the treatment rapidly, reporting less pain leading to reduction of analgesics, and the new metastasis disappeared. Furthermore, lactate dehydrogenase and liver transaminase ASAT had decreased 4 days after the initiation of the treatment and continued to descend until they reached normal levels 1 month later. The patient complained of itches and exanthema, which were interpreted as adverse effects of the treatment and disappeared 1 week later. She also suffered from nausea.

The patient underwent frequent ultrasound and Doppler examinations in order to monitor the development of the fetus. At the initiation of the treatment the intrauterine growth already showed a 9% descend compared with the previous control that was performed a week before. The restricted growth continued for the next month (mostly affecting the body and not the head) and dropped to -34%, compared with the normal intrauterine growth curve. The decision was then taken to deliver the fetus through caesarian section at the 30th week of gestation. The 1,028 g newborn infant had an uncomplicated stay at the neonatal ward, and was discharged home in good condition. Blood samples from the mother, the newborn, and the umbilical cord were tested for the presence of vemurafenib. According to these results, the infant had a plasma value of 10.9 µg/mL, the same as the sample from the umbilical cord. The maternal value was 24.3 µg/mL.

Two months postpartum a computed tomography scan of the mother due to increasing nausea showed metastatic lesions in the cerebrum and dura. Radiation therapy was planned, however that treatment requires at least a week free of vemurafenib according to the manufacturer. During that week the disease progressed rapidly, with neurological symptoms dominating the clinical image. Two radiation fractions were given without significant symptomatic improvement. The patient died 3.5 months after the initiation of the treatment with vemurafenib.

### Discussion

We report on a pregnant patient with advanced MM who responded immediately after initiation of vemurafenib treatment, which was reflected in clinical improvement followed by normalization of hematological and biochemical tests. The patient had a 3-month progression-free survival, with the delivery, 5 weeks after

the initiation of treatment, of a healthy newborn at the 30th week of gestation.

According to the registration trial, patients with metastatic MM who received vemurafenib had a median progression-free survival of 5.3 months (median),<sup>2</sup> which is superior to the 3-month period experienced by our patient. A crucial factor to consider for anticancer therapy during pregnancy is the normal development of the fetus. The risk of congenital malformations is not increased if cytotoxic treatment is administered after the period of embryogenesis. Instead, a high incidence of neonatal bone marrow insufficiency after prenatal chemotherapy exposure has been described.<sup>4</sup> Vemurafenib belongs to a new class of anticancer agents and has not been associated with teratogenesis in animal studies. Available data suggest that the impact on fetal growth might be related to specific cancer types and treatments. At present, it is recommended that anticancer treatment should be initiated and sustained during pregnancy until viability of the fetus is reached. Moreover, prolonged therapy is preferably considered until at least the 35th week of gestation in order to improve the prognosis.<sup>5</sup> A Swedish national multicenter study has shown markedly increased 1-year survival of premature infants born at the 26th week of gestation instead of the 22nd week.<sup>6</sup>

In the present case, treatment with vemurafenib was initiated at the 25th week of pregnancy in order to prolong the duration of gestation until week 34. Metastases of MM to the placenta have been reported but fetal involvement is uncommon.<sup>7</sup> In our case, ultrasound and postpartum placenta examination revealed no metastatic lesions in the placenta. A possible complication of treatment with vemurafenib is the induction of high-grade squamous cell carcinoma of the skin to the fetus but there were no signs of skin tumors in this case.

The patient was followed-up on a weekly basis by obstetricians in order to monitor fetal growth. A restriction of growth was observed already at the 24th week of gestation, before the initiation of the vemurafenib therapy. This growth restriction was likely a result of maternal illness associated with malnutrition and catabolic status. Despite a pronounced antitumoral treatment effect, the fetal growth curve did not return to normal. At this stage, a toxic effect of vemurafenib treatment as a contributing factor for the inhibition of growth cannot be ruled out.

Mean predose exposure for the standard dose given to the patient is 50  $\mu\text{g}/\text{mL}$ .<sup>8</sup> In the present case, the mother had a serum concentration of 24.3  $\mu\text{g}/\text{mL}$ , which is 50% lower than that value, however, interpatient variability should be taken under consideration. In addition, pregnant women taking vemurafenib might have lower serum concentrations in general. In animal experiments fetal concentrations of the active substance taken 4 hours after dosing were 3% to 5% of the maternal concentration, indicating that vemurafenib crosses the placenta only to a limited extent. In our case, the newborn infant had a

serum drug concentration of (10.9  $\mu\text{g}/\text{mL}$ ), which was approximately 50% of the maternal concentration, markedly higher than could be expected from the animal experiments. Negative impacts of this exposure—besides growth inhibition—are possible, at the same time as one could speculate in a positive effect in preventing fetal MM spreading.

The incidence of MM is growing and women in childbearing ages are frequently affected. Treatment with vemurafenib is a rising anticancer therapy, however it has previously not been studied during pregnancy. In this case, the patient had a 3-month progression-free period, which enabled prolonged gestation and delivery of a healthy baby at week 30. The baby is until now free of complications as well as of metastatic MM. Full neurological follow-up due to prematurity and the vemurafenib exposure is planned 1 year after delivery.

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#### **AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The author(s) indicated no potential conflicts of interest.

#### **REFERENCES**

1. Tarhini AA, Agarwala SS: Cutaneous melanoma: Available therapy for metastatic disease. *Dermatol Ther* 19:19-25, 2006
2. Chapman PB, Hauschild A, Robert C, et al: Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 364:2507-2516, 2011
3. Morice P, Uzan C, Uzan S: Cancer in pregnancy: A challenging conflict of interest. *Lancet* 379:495-496, 2012
4. Pentheroudakis G, Pavlidis N: Cancer and pregnancy: Poena magna, not anymore. *Eur J Cancer* 42:126-140, 2006
5. Van Calsteren K, Heyns L, De Smet F, et al: Cancer during pregnancy: An analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. *J Clin Oncol* 28:683-689, 2010
6. Fellman V, Hellstrom-Westas L, Norman M, et al: One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA* 301:2225-2233, 2009
7. Baergen RN, Johnson D, Moore T, et al: Maternal melanoma metastatic to the placenta: A case report and review of the literature. *Arch Pathol Lab Med* 121:508-511, 1997
8. Flaherty KT, Puzanov I, Kim KB, et al: Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med* 363:809-819, 2010

DOI: 10.1200/JCO.2012.45.2870; published online ahead of print at [www.jco.org](http://www.jco.org) on February 11, 2013