



# Treatment of metastatic malignant melanoma during pregnancy with a BRAF kinase inhibitor: A case report

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## ABSTRACT

**Background:** Melanoma accounts for 8% of all malignancies encountered during pregnancy. BRAF kinase inhibitors have shown promise in the treatment of late-stage melanoma; however, there have been no studies and only one previous case report regarding its use in pregnancy.

**Case:** A 25-year-old woman, gravida 1, at 20 weeks of gestation presented to the clinic with a complaint of a lump on her neck and dyspnea. She had had a melanoma that was surgically treated 5 years prior to her pregnancy. A biopsy was performed and she was found to have metastatic melanoma. After multidisciplinary discussion, the patient was offered treatment with vemurafenib, a BRAF kinase inhibitor, and the mass reduced in size.

**Conclusion:** Malignancy during pregnancy poses both medical and ethical dilemmas in the management and treatment of cancer. The treatment of late-stage melanoma in pregnancy with a BRAF kinase inhibitor may be an option.

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## 1. Introduction

Cancer during pregnancy is uncommon, affecting approximately 1 in 1000 pregnancies. Of those pregnancies complicated by cancer, either pre-existing or diagnosed during pregnancy, melanoma accounts for 8%. Melanoma represents 25% of cancers that are diagnosed during pregnancy [1]. Cancer during pregnancy has the potential to metastasize to the placenta and fetus. Although it is rare, melanoma is the most common cancer to metastasize to the placenta and fetus. The incidence of melanoma in the general population is increasing and approximately one-third of women diagnosed with melanoma are of child-bearing age [1,2].

From the 1950s to 1980s, several case reports, case control studies and large population-based cohort studies suggested that pregnancy-associated melanoma may lead to worse maternal outcomes and decreased survival; however, these studies did not take account of a sufficient array of prognostic factors to include an examination of stage of disease [1,2]. A recent population-based Swedish study compared cause-based mortality among women with pregnancy-associated melanoma with that of women diag-

nosed with melanoma not associated with pregnancy and found no difference after adjustment for prognostic factors [1]. Multiple studies have also examined women who were diagnosed with melanoma prior to pregnancy and pregnancy did not appear to have an effect on prognosis.

The treatment of melanoma during pregnancy creates complex medical decision making. One must consider optimal maternal treatment benefit as well as the potential harmful effects on the fetus. Approximately 40–60% of advanced-stage melanomas are found to have a BRAF mutation [3]. The BRAF gene encodes the B-raf growth signal transduction protein kinase. BRAF kinase activates the mitogen-activated protein kinase pathway sending signals to cells directing cell growth and differentiation. Mutated forms of BRAF lose the ability to regulate cell growth and differentiation, leading to tumorigenesis. BRAF kinase inhibitors block this pathway of cellular proliferation, thereby inhibiting tumor growth. Treatment with BRAF kinase inhibitors (such as vemurafenib) increases the median survival of patients with late-stage melanoma compared with other treatments [3]. Because the majority of patients with advanced-stage melanoma have this mutation, BRAF kinase inhibitors have become a promising treatment option. However, there are no studies regarding its use in pregnancy. There has been only one previous case report of BRAF kinase inhibitor use in pregnancy for the treatment of advanced-stage melanoma [4].

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## 2. Case

A 25-year-old woman, gravida 1, presented to clinic at 20 weeks of gestation with a complaint of a lump on the right side of her neck and dyspnea. A chest x-ray was obtained and identified bilateral pulmonary nodules that were suspicious for metastasis. A biopsy of the neck lesion was performed and tissue exam revealed metastatic melanoma. Five years previously she had had a stage IIA melanoma diagnosed and treated with wide local excision and sentinel lymph node biopsy, which was negative.

The patient was counseled that the pregnancy would limit treatment options and so likely affect her prognosis. She was offered termination of the pregnancy, treatment during pregnancy or expectant management. She declined termination and chose to begin treatment after fetal viability had been reached. After a multidisciplinary discussion between maternal fetal medicine and oncology, the patient was offered vemurafenib as treatment, as it has shown the greatest benefit on median survival for patients with late-stage melanoma. She was counseled extensively that vemurafenib had not been widely used in pregnancy and fetal effects were unknown, although no adverse outcomes had been noted in animal studies. The patient accepted these risks and chose to undergo treatment.

Treatment with vemurafenib was started after fetal viability had been achieved per the patient's wishes (at 25 weeks of gestation). She was followed closely with surveillance and frequent ultrasound scans by maternal-fetal medicine specialists for fetal growth assessment and evaluation of the placenta. After discussion with the multidisciplinary team, induction of labor was scheduled at 34 weeks due to the recommendation for additional chemotherapeutic agents to treat her metastatic melanoma. Betamethasone 12 mg intramuscular injection, 2 doses 24 h apart, was administered for fetal lung maturity 1 week prior to induction of labor.

She had an uncomplicated vaginal delivery of a female infant with a birth weight of 2510 g (67th percentile) and APGAR scores of 9 and 9. The placenta was sent to pathology for review and there was no evidence of placental metastasis. The neonatal course was complicated by paroxysmal supraventricular tachycardia and required admission to the NICU. The infant was treated with a beta-blocker, which controlled the paroxysmal supraventricular tachycardia, and the infant was discharged home on this medication with appropriate follow-up.

The patient had a fairly good maternal outcome with an uncomplicated pregnancy and delivery. Following delivery, she received 2 cycles of ipilimumab and nivolumab. A CT scan performed at 3 months postpartum showed interval decrease in the size of the pulmonary nodules, mediastinal and hilar lymph nodes and of several subcutaneous nodules. She is currently continuing surveillance with oncology. Her prognosis is poor. The reported 5-year survival rate in patients with stage IV metastatic melanoma is 15–20% and 3% 10-year survival rate is reported for patients with lung metastasis [5].

## 3. Discussion

This case involved a pregnant patient with advanced-stage melanoma which was treated with vemurafenib during pregnancy and resulted in reduction of the size of her pulmonary and cutaneous metastases. One other case of melanoma treated with vemurafenib during pregnancy is reported in the literature; however, in that case the patient did not respond to treatment and the fetus was noted to have progressive fetal growth restriction.

The management of cancer during pregnancy is challenging and requires a multidisciplinary team approach. The risks and benefits to both mother and fetus have to be considered. Until the

introduction of targeted immunotherapy, chemotherapy was the only treatment for metastatic melanoma. New therapies, such as ipilimumab, nivolumab, pembrolizumab and vemurafenib, have improved the median survival of patients with advanced-stage disease and are now the initial treatment of choice. The effects of these drugs on fetal development are unknown, as there have been no clinical trials. Ipilimumab (IgG1) has been shown to have placental transfer in animal studies and produced an increase in the incidence of miscarriage, stillbirth, preterm births and neonatal death in monkeys [6].

Nivolumab and pembrolizumab (IgG4) have not been described in humans during pregnancy; however, in mice it has been associated with fetal loss, presumably due to downregulation of T-cell function that is required to maintain immunotolerance of pregnancy. Vemurafenib, a BRAF inhibitor, has not been associated with adverse pregnancy outcomes in animal studies (4). Its use has been reported in one case of metastatic melanoma during pregnancy, in which progressive fetal growth restriction was noted. However, fetal growth remained normal in our case; therefore, it is unknown whether vemurafenib was the cause in the first case.

The effect on normal fetal development and growth needs to be considered when treating cancer in pregnancy. The risk of congenital malformations is not increased when treatment is initiated after embryogenesis. However, as discussed above, there is concern about the risk of cancer treatment and its association with fetal growth restriction, preterm birth and fetal death. BRAF inhibitors block cellular proliferation, which in theory could affect fetal growth; however, this was not observed in animal studies or in our case. Growth scans were performed throughout our patient's treatment and appropriate growth was noted throughout the pregnancy. The infant was developed paroxysmal supraventricular tachycardia after birth, but it is not known whether this was an effect of vemurafenib.

Malignancy during pregnancy poses both medical and ethical dilemmas. The incidence of melanoma is increasing and one-third of women affected are of child-bearing age [1,2]. Many treatments for advanced-stage disease have not been studied in pregnancy. Vemurafenib is now one of the initial treatments of choice for metastatic melanoma but it has not been studied in pregnancy. This patient had an optimal outcome with delivery of a healthy infant and decrease in size of her pulmonary and cutaneous metastasis during her pregnancy, while receiving treatment with vemurafenib. Treatment of metastatic melanoma in pregnancy with a BRAF inhibitor may be an option.

## Contributors

Megan Pagan was the main author, conducted the literature review, and reviewed and revised the manuscript.

Heather Jinks assisted in writing the manuscript, reviewing the literature, and reviewing and revising the manuscript.

Mark Sewell was staff mentor, and assisted in writing, reviewing and revising the manuscript.

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## Patient Consent

Obtained.

**Provenance and Peer Review**

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**Presentation**

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**Declaration of Competing Interest**

The authors declare that they have no conflict of interest regarding the publication of this case report.

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