A pregnant patient with ALK-positive non-small cell lung cancer treated with alectinib: A case report and review of the literature

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Abstract. Oncogenic rearrangements in the anaplastic lymphoma kinase (ALK) gene account for 5% of non-small cell lung cancer (NSCLC) cases. ALK inhibitors have markedly improved the outcome of metastatic ALK-positive NSCLC (ALK$^+$ mNSCLC) by increasing long-term overall survival. Although a diagnosis of NSCLC during pregnancy or the peripartum period is rare, ALK$^+$ NSCLC accounts for 38% of NSCLC cases in women of childbearing age (18-45 years old). The younger age and prolonged survival of patients with ALK$^+$ mNSCLC bring new challenges for lung cancer and obstetrics research, and raises questions related to pregnancy and family planning. The present study described normal fetal development and no obstetric complications in a patient infected with HIV diagnosed with ALK$^+$ mNSCLC, who became pregnant during treatment with alectinib, a third-generation ALK inhibitor.

Introduction

Lung cancer is the second most common and most lethal malignancy worldwide (1) The development of targeted therapies against oncogenic driver alterations of NSCLC, which affect several kinases, has significantly improved outcomes of NSCLC, including for instance in ALK$^+$ mNSCLC (2). Oncogenic rearrangements in the anaplastic lymphoma kinase gene (ALK) account for 5% of non-small cell lung cancer (NSCLC) (3-5).

ALK positive NSCLC represent 8% of all lung cancers in never-smoker patients (6) Treatment with an ALK inhibitor has significantly improved the outcome of metastatic ALK positive NSCLC (ALK$^+$ mNSCLC) patients with median long term overall survival to 81 months (7) Therefore, ALK inhibitors have become a standard form of care in ALK$^+$ mNSCLC (8). However, pregnant women are deprived of using this drug, instructions of use stating that ALK inhibitors are contraindicated during pregnancy (9).

Based on findings from animal studies and its mechanism of action, alectinib can cause fetal harm when administered to pregnant women. Administration of alectinib to pregnant rats and rabbits during organogenesis period resulted in embryo-fetal toxicity and abortion at maternally toxic doses with exposures approximately 2.7 times of those observed in humans with alectinib 600 mg twice daily. Fetal loss, low fetal weight and malformations (vertebrae, thymic cord, ventricle, ureter and subclavian artery) were reported (8). Effective contraception during treatment and for several months after the last dose of ALK inhibitors is thus recommended. Although a diagnosis of NSCLC during pregnancy or the peripartum period is rare, ALK$^+$ NSCLC accounts for 38% of NSCLC in women of childbearing age (18-45 years old) (10). Furthermore, ALK$^+$ NSCLC represent 12.5% of NSCLC diagnosed during pregnancy or peripartum (10). Younger age and prolonged survival of ALK$^+$ mNSCLC bring new challenges in this field, including questions associated with pregnancy and family planning. We present the case of fetal exposure to alectinib in an HIV infected patient diagnosed with ALK$^+$ mNSCLC.

Case report

An HIV infected, 24-year-old non-smoking patient was diagnosed in April 2019 at the Clinique Saint-Pierre (Ottignies, Belgium) with ALK$^+$ mNSCLC cT2bN3M1c (axillary and

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subdiaphragmatic nodes, no brain metastasis). Therapy with alectinib 600 mg twice daily was initiated. The patient is treated by Symtuza®, a combination of darunavir, cobicistat, emtricitabine and tenofovir alafenamide. The HIV viral RNA blood load was negative. The lung biopsy analysis identified an ALK translocation, low expression of programmed death ligand 1 (PD-L1) and no epidermal growth factor receptor (EGFR) mutation. Effective contraception was recommended to prevent pregnancy during treatment but the patient refused all forms of contraceptive method.

Her disease was stabilized after 6 months of treatment without any adverse event, even in combination with the retroviral treatment. Then, a pregnancy at 22 weeks of gestational age was diagnosed. Alectinib treatment was continued despite a formal contraindication. The patient was referred to a tertiary center at 27 weeks and 5 days of pregnancy. A multidisciplinary board consisting of medical oncologists, obstetricians and pneumologists recommended stopping alectinib treatment until the end of the pregnancy due to the teratogenic risks as well as the risk of cognitive, psychological and psycho-motor development disorders.

Fetal ultrasounds showed normal fetal growth and morphology as well as placental aspect. Finally, the patient decided to stop alectinib at 32 weeks of gestation.

A fetal magnetic resonance imaging (MRI) at 32 weeks did not show any developmental or cerebral abnormalities (Fig. 1).

Labor was induced at 36+6 weeks of gestation and a eutrophic girl with an Apgar score of 7 at 5 min and 10 at 10 min was born. The placenta histopathology did not show any mutations or metastatic invasion by cancerous cells (Figs. 2 and 3). Neonatal HIV PCR-test was negative. The child is being monitored on a regular basis for any behavioral or cognitive delays.

Alectinib treatment was reintroduced on the day after the delivery. A CT scan (Fig. 4) and brain imaging showed stable disease. To this day, the patient is tolerating the treatment well.

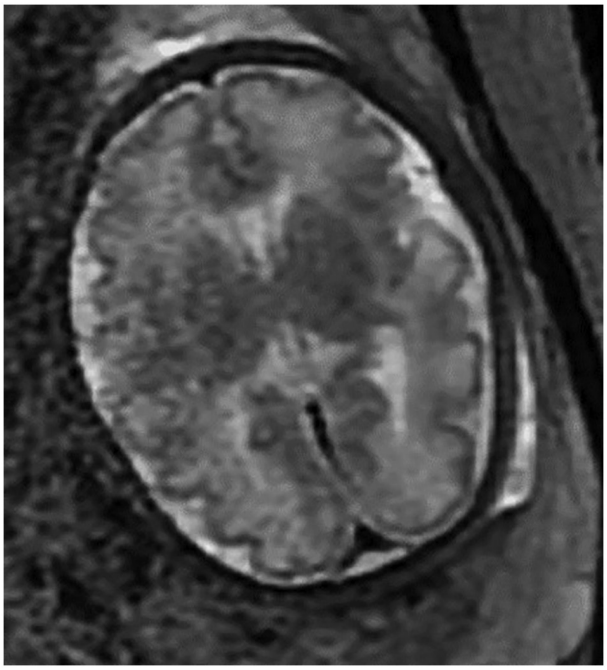

Figure 1. Fetal magnetic resonance imaging at 32 weeks, axial view of the fetal brain (TSE, T2), normal gyration and brain parenchyma.

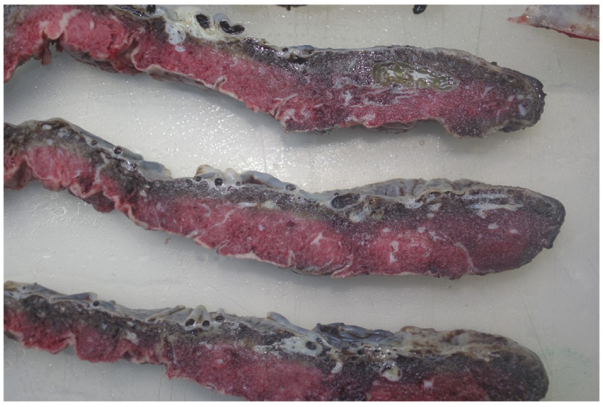

Figure 2. Macroscopical evaluation of placental plate was normal and did not show any lesion.

Discussion

We present a case of ALK+ mNSCLC lung cancer in combination with unplanned pregnancy. The alectinib treatment was started a few months before the pregnancy, resulting in a good response and stability of the disease. It was discontinued at 32 weeks. In absence of safe administration during pregnancy, alectinib is not recommended during pregnancy. Lung cancers are mostly treated by surgery, chemotherapy, radiotherapy and systemic therapy (11,12).

Surgery is not uncommon during pregnancy and needs close collaboration between surgeons, anesthesiologists, gynecologists and pediatricians. Surgeries under local or general anesthesia are performed during pregnancy, but non-emergent procedures should be postponed until after the first trimester to avoid miscarriages (13,14). Chemotherapy can be administered after the first trimester of pregnancy (15). The short and long-term child development, the cognitive behavior and the cardiac function seem to be reassuring (16,17). Radiotherapy for curative or palliative treatment is also feasible after the first trimester of pregnancy while balancing the fetal and maternal risks (18). Immunotherapy affects the pregnant woman's immune system, so that materno-fetal adverse outcomes may occur. Therefore, it is not recommended during pregnancy and should be discussed case by case (19). Treatment by alectinib is nevertheless not recommended during pregnancy because of rarity of cases.

Over the last years, cancer incidence among pregnant women is increasing due to a high rate of smokers and an increased maternal age (20-24). Although mild side-effects with this targeted therapy are observed, pregnancy is discouraged considering the fetal toxicity observed in preliminary animal studies. Regarding the paucity of these cancers during pregnancy, these treatments are currently not recommended (22).

Although a diagnosis of NSCLC during pregnancy or the peripartum period is rare, ALK+ NSCLC represents 38% of NSCLC diagnosis performed in women of childbearing age (10). Because pregnant women are excluded from almost all clinical trials, available data on the teratogenic risks of tyrosine kinase inhibitors including ALK inhibitor are limited to case reports and animal studies.

Table I: Clinicopathologic features of ALK+ MNSCLC lung cancers reported in literature.

First author, year	Lung tumor type and diagnosis	Treatment during pregnancy	Antineoplasic treatment during pregnancy	Timing of delivery	Fetal outcome	Maternal outcome	Follow-up in years	(Refs.)
Present study	ALK+ NSCLC, diagnosis before pregnancy	Alectinib and HIV treatment	Start of pregnancy until 32 weeks	36+6 weeks	Normal, 19 months	Alive	1.6	-
Scarfone, 2021	ALK+ lung adenocarcinoma diagnosis before pregnancy	Alectinib	Whole pregnancy	35+5 weeks	Normal, 32 months	Alive, mother in partial remission	2.6	(27)
Komura, 2018	Lung adenocarinoma ALK+ diagnosis after delivery	No	No treatment	37 weeks	Normal, 12 months	Alive	1	(22)
Neves, 2014	ALK+ lung adenocarcinoma diagnosis at 27 weeks	Corticosteroid injection for fetal lung maturation	No treatment	29 weeks	Normal at 19 months	Progression-free survival of 9 months	Died 19 months after diagnosis	(23)
Sariman, 2013	ALK+ lung adenocarcinoma diagnosis after delivery	Antibiotics for pneumonia	No treatment	28 weeks	NA	Stable at 6 months	NA	(24)

ALK, anaplastic lymphoma kinase gene; NSCLC, non-small cell lung cancer; NA, not available.

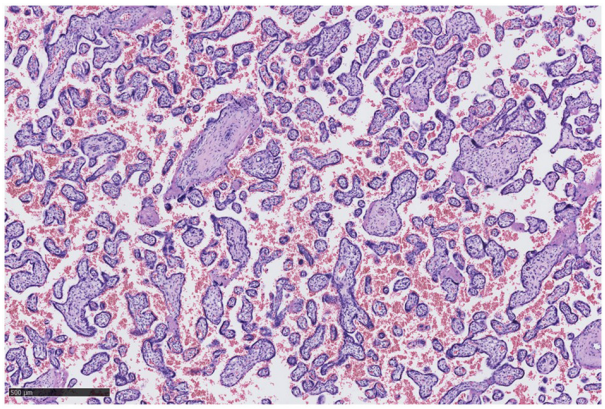

Figure 3. The histological evaluation is characterized by normal developed villi on regard of the gestational age. No signs of thrombosis, inflammation or infiltration by the tumor have been observed (Hematoxylin and eosin; magnification, x5).

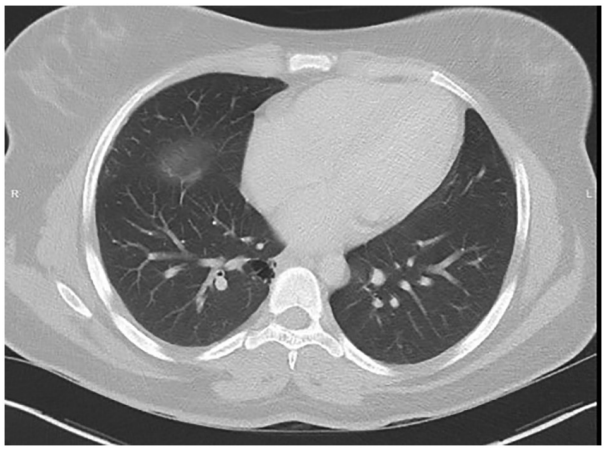

Figure 4. Chest CT scan postpartum: Stability of the lung lesions.

The European Society for Medical Oncology (ESMO) recommends close monitoring until the second trimester. If urgent treatment is required, pregnancy termination should be discussed. In the last trimester, preterm delivery or initiation of carboplatin plus weekly dose of paclitaxel is therefore recommended in the context of lung cancer (25). The young age of patients in the context of prolonged survival of ALK+ mNSCLC raises new questions associated with maternity and family planning of these patients.

The ALK inhibitor may impact not only the fetal development but also the cognitive (memory impairment, disturbance in attention, and amnesia) and psychological development (anxiety, depression, and affect lability) of the child (26). Only one other case of pregnancy during an alectinib treatment has been described in the literature, with a continuation of the treatment until delivery. The fetal and child development until 20 months were normal and uneventful (27). The balance between fetal and maternal benefits and risks illustrates the dilemma faced in this specific and rare situation. Breastfeeding

was discouraged according to drug maker recommendations. Other cases reports with ALK^+ lung tumors associated with pregnancy are summarized in Table I.

Our case also shows the importance of including the patient in the treatment decision. Despite being advised of the risks, the patient decided to become pregnant regardless of the potential consequences for her and the child and to continue the treatment until 32 weeks of pregnancy. This case illustrates a normal pregnancy under ALK-inhibitor without fetal and placental abnormalities and no relapse of the mother at one year after the birth. Given the rarity of case reports and information on fetal adverse effects, further analysis is needed to confirm these observations and this positive feto-maternal development.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MMG and FDS conceived the idea for this paper. MMG, FDS, FD, LC, PB, FAN, PC and VB collected the data. FDS, MMG, LC, PB, FAN and PC prepared, created and wrote the initial draft. MGM drafted the figure. MMG, FDS, FD and FA analyzed the data. MMG, FDS and FD confirm the authenticity of all the raw data. MMG, FDS, FDLC, PB, FAN, PC, VB, FA and MMG wrote and reviewed the draft. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethical Committee of the Cliniques Universitaires Saint-Luc, Brussels (Belgian number 2014/28Mar/142). Patient data were registered after written informed consent.

Patient consent for participation

The patient consented to the data and images being taken for the purpose of research and also consented to their publication.

Competing interests

The authors declare that they have no competing interests.

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