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Case reports

# Efficacy and safety of gefitinib during pregnancy: Case report and literature review

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ABSTRACT

The incidence of lung cancer is rising in pregnancy, which is diagnosed on stage III–IV in 98%. Almost half of these patients are non-smokers, who are associated with more epidermal growth factor receptor (EGFR)-mutated lung cancer. As cytotoxic chemotherapy is associated with poor outcome for mothers and prematurity for children this will probably lead to repeatedly question the use of EGFR-Tyrosine kinase inhibitors (TKI) (i.e. gefitinib and erlotinib) during pregnancy for EGFR-mutated lung cancer. EGFR-TKIs are recommended as the first line targeted therapy in case of advanced non small cell lung carcinoma (NSCLC) with an activating EGFR mutation but not recommended during pregnancy due to lack of data.

We report clinical and pharmacological data for gefitinib during pregnancy in both the mother and fetus and resume the literature on the subject. A 33-year-old pregnant mother exhibited a disseminated EGFR-mutated lung carcinoma with respiratory distress at 26 weeks of pregnancy. Gefitinib administration was associated with rapid maternal respiratory improvement allowing a planned cesarian section on week 35, giving birth to a healthy baby (2575 g) with regular development at 24 months of follow-up. The mother exhibited a progression-free survival of 42 weeks with an overall survival of 22 months.

Gefitinib residual concentration was found in cord blood at 25.7 ng/mL, confirming a transplacental transfer, but at only 20% of the maternal concentration measured at the same time (i.e. 127.1 ng/mL). Gefitinib concentration in amniotic fluid, which represents chronic fetal exposure to the drug, was also 20% of the maternal residual concentration (16.9 ng/mL) and reflected no fetal accumulation of the drug, despite both long half time elimination of gefitinib (i.e. 48 h) and long time exposure (i.e. 55 days). This low transplacental transfer is an important report, as potential side effect toxicity on the fetus is likely correlated to gefitinib blood concentration.



## 1. Objectives

Frequency of lung carcinoma in pregnancy is unknown but increasing due to the augmentation of both tobacco consumption in young women and the mean age of pregnancy [1]. Diagnosis is delayed due to pregnancy and mostly made at stage III–IV (58 of the 59 cases described in literature) [2]. Identification of an activating epidermal growth factor receptor (EGFR) mutation, usually on exon 18 or 19, in advanced lung cancer leads to EGFR-Tyrosine kinase inhibitor (TKIs) (i.e. gefitinib and erlotinib) prescription as first line-targeted therapy. Indeed EGFR-TKIs increase the progression-free survival with fewer side effects than cytotoxic chemotherapy [3]. However pharmacological data for EGFR-TKIs in both pregnant women and fetuses as well as long term follow up of exposed children have not been reported. This led to guidelines recommending cytotoxic chemotherapy as the gold standard during pregnancy despite a constant poor prognosis for maternal survival and an

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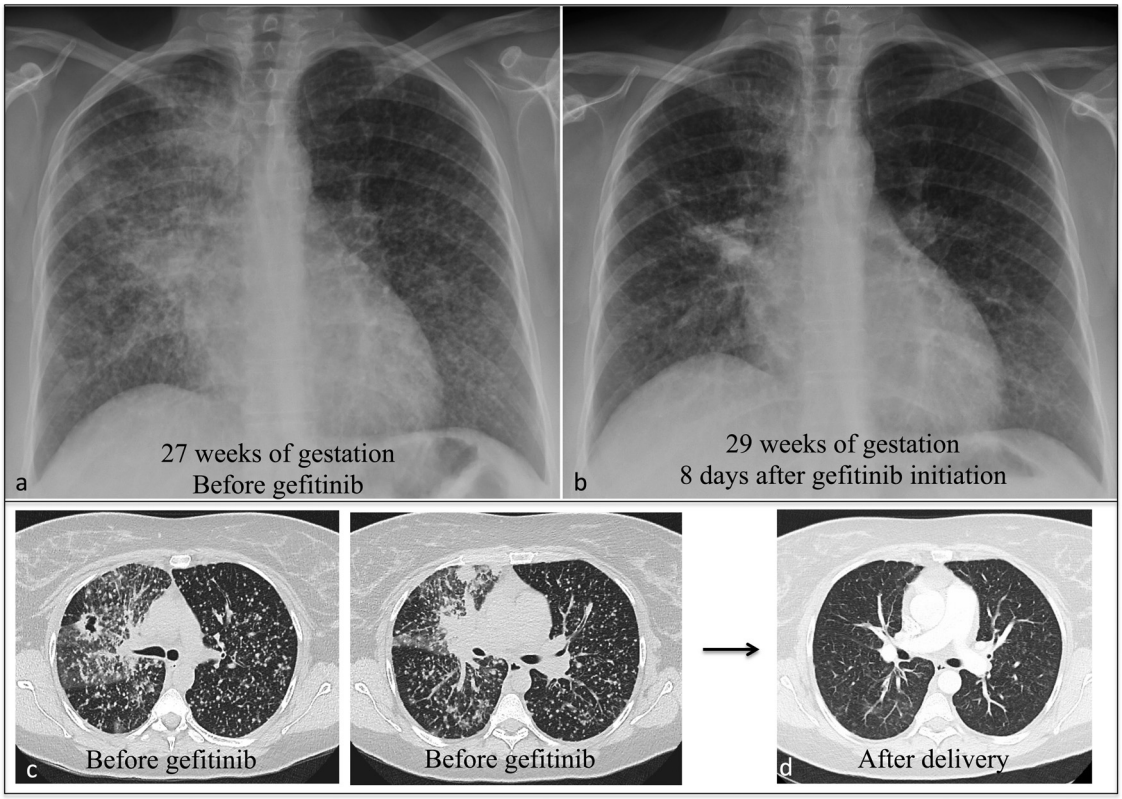


**Fig. 1.** (a) Chest radiograph before the beginning of gefitinib when patient required 3 L/mn of oxygen supplementation. (b) Reflects change after one week of gefitinib administration when patient is breathing room air. (c and d) Exhibit chest CT-scan at diagnosis and immediately after delivery when patient had received gefitinib for two months.

increase of prematurity which is the main cause of poor outcome in children [1,2,4,5]. We present the first case with pharmacokinetic assays of a pregnant woman receiving gefitinib for a stage IV lung adenocarcinoma with EGFR activating mutation and a follow-up of 24 months of both mother and child.

## 2. Case report

A 33-year-old female at 26 weeks of gestation experienced progressing dyspnea with a dry cough for 2 months. The chest radiograph exhibited a bilateral pulmonary infiltrate leading to her hospitalization. She had smoked for 3 years, for a total of 1 pack-year, then stopped ten years ago. Physical and obstetrical examinations were normal. A chest CT showed diffused micronodules, peribronchovascular thickening, a hilar enlargement and two masses including one excavated (Fig. 1c). As no endoluminal tumor was seen on fiberoptic bronchoscopy the diagnosis of lung adenocarcinoma was obtained on a CT-guided percutaneous needle biopsy of the consolidation. The EGFR activating mutation was positive on exon 19. The mother experienced rapid clinical respiratory worsening with transcutaneous oxygen saturation at 86% on room air and required 3 L/mn of oxygen to obtain a saturation above 92%. Chest radiograph worsened with diffuse extensive bilateral opacities (Fig. 1a). During the multidisciplinary consultation we opted for EGFR-TKI treatment. Gefitinib 250 mg/d was initiated at 28 weeks of gestation. From the eighth day of Gefitinib the patient exhibited dramatic improvement and ceased oxygen with a major reduction of the pulmonary infiltrate on chest radiograph (Fig. 1b). Fetal growth, morphology and amniotic fluid index, evaluated on twice-monthly trans-abdominal ultrasonography, were normal. Treatment duration with gefitinib until delivery was 55 days. The steady state residual concentration of gefitinib (i.e. pre-dose intake) of the mother before delivery was 83.2 ng/mL. The patient was delivered by planned cesarean section at 35 weeks of gestation of a healthy baby of 2575 g, Apgar score 4/9/10, pH 7,31. The placenta, which weighed 520 g, was normal. At delivery, 16.5 h after last oral intake of Gefitinib, its concentrations were 127.1 ng/mL in maternal plasma, 25.7 ng/mL in cord blood, and 16.9 ng/mL in amniotic fluid. The progression-free survival (PFS) with gefitinib was 42 weeks. After progression, confirmed on CT scan, erlotinib was unsuccessfully tried during 6 weeks then a combination of cisplatine with pemetrexed was used. Combining all these therapies allowed an overall survival of 22 months. Child follow up at 24 months exhibited regular development.

## 3. Discussion and review of literature

### 3.1. Therapeutic discussion

Lung cancer during pregnancy is a growing issue due to its constant rise, linked to increase in tobacco consumption and the mean age of pregnancy [6]. There is also a rise in the proportion of lung cancer in non-smokers (or light smokers like our patient), in particular in case of pregnancy, where it can reach more than 40% in published cases [2,6]. This could be relevant as the proportion of EGFR-mutated lung cancer is higher in the non-smoking subgroup [6].

Pregnant patients are diagnosed with advanced lung cancer in 98% of cases that can lead, as in our case, to rapid respiratory distress which weighs heavily on therapeutic options [2,6]. Data on lung cancer are absent or under-represented in series of cancers during pregnancy published in literature [4]. Yet lung cancer seems apart from other cancers as it can cause respiratory distress leading to a constant poor short term prognosis for mother and preterm birth despite use of cytotoxic chemotherapy, highlighting its poor efficiency in this particular condition [2] As