Successful Treatment of Non–Small Cell Lung Cancer With Erlotinib Throughout Pregnancy

Erlotinib is the standard of care for epidermal growth factor receptor (EGFR) mutated lung adenocarcinomas in the United States. However, in pregnant patients with lung cancer, chemotherapy is recommended, irrespective of EGFR mutations, given the lack of experience and uncertainty for fetus’s safety with erlotinib.

Methods | The patient, with twin pregnancy after in vitro fertilization, was intentionally treated with erlotinib. Pharmacokinetics of erlotinib were measured in the mother’s plasma and the twins’ cord blood, which were collected at delivery. The pharmacovigilance of erlotinib during pregnancy was analyzed by accessing the Roche/Genentech global database.

Results | A patient, a nonsmoking woman in her forties who was 10-weeks pregnant with dichorionic-diamniotic twins, was diagnosed as having a stage IV exon 19 deletion adenocarcinoma after a generalized seizure. The primary tumor in the right lung was 5.1 cm, with an additional smaller lesion in another lobe, and 6 cerebral metastases. After an ethics consultation, she decided to continue the pregnancy. Her brain lesions were treated by stereotactic radiotherapy during the first trimester, with adequate precautions against uterine radiation. She started erlotinib, 150 mg daily, at the start of the second trimester under close surveillance by medical oncology and obstetrics. The only adverse effects were mild skin rash and fatigue. At 33 weeks, intrauterine growth restriction (IUGR) was diagnosed in 1 twin, leading to a cesarean delivery at 37 weeks. The treatment duration of erlotinib during pregnancy was 130 days. Erlotinib was held 72 hours prior to delivery and resumed 3 weeks postpartum after proper healing. The female twins weighed 2353 and 2438 g, which were small weights for this gestational age (87% of expected) but comparable with weights of other fetuses exposed to chemotherapy. Placental pathologic evaluation revealed no metastasis. The aspartate transaminase level (Figure) was elevated, but alanine transaminase and alkaline phosphatase levels were normal. Imaging assessments at baseline and 4 weeks postpartum demonstrated a partial response to the chemotherapy. Both lung lesions became cystic, and all brain lesions were smaller. To date, at 13 months postpartum, the patient continues to receive erlotinib and works full-time. Both twins were thriving at the 12-month developmental milestone.

Erlotinib and its active metabolite, OSI-420, were measured in the mother’s plasma at 54 ng/mL, which is about 5% of the expected plasma concentration for daily erlotinib—150 mg—at steady state.1 Drug concentrations were lower in cord blood, confirming transplacental transfer, around 25% (erlotinib) and 10% (OSI-420) of the maternal plasma concentration (Figure).

Discussion | For pregnant patients with lung cancer, the standard of care is chemotherapy during the second and third trimesters, but the prognosis is poor. In a series of 9 cases, all patients died within 1 year of delivery.2 Novel cancer treatments pose therapeutic and ethical challenges. This first pharmacological report of erlotinib in pregnancy demonstrates low-
efficiency transplacental transfer, as already shown for gefitinib. Pharmacokinetic parameters affecting placental drug transfer include molecular weight, ionization constant, lipophilicity, and protein binding. A low efficiency of placental transfer decreases fetal exposure and potential toxic effects. However, reversible liver toxicity and IUGR were observed.

The Roche/Genentech pharmacovigilance worldwide database has logged 1,214,065 patients receiving commercial or experimental (clinical trials) Erlotinib. Eighteen cases were in pregnant women, with known outcome for 8 pregnancies (Table). There were 4 therapeutic abortions, and 4 women delivered normal newborns. In the case of the longest exposure (33 weeks), IUGR with oligohydramnios was observed, but the newborn was normal. IUGR was also noted in one twin. Prolonged exposure to erlotinib during pregnancy might be associated with IUGR.

Current literature and pharmacovigilance data did not demonstrate congenital abnormalities in erlotinib exposed pregnancies (including first trimester exposure), but IUGR and liver toxic effects remain a concern. EGFR tyrosine kinase inhibitor also yields a survival advantage over cytotoxic chemotherapy in pregnant women with EGFR-mutated lung cancer and should be considered.

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Table. Analysis of Pregnant Women Exposed to Erlotinib—Data From the Roche/Genentech Pharmacovigilance Database

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Mother’s Age, y</th>
<th>Pregnancy Stage at Exposure</th>
<th>Duration, wk</th>
<th>Other Cancer Treatment</th>
<th>Outcome</th>
<th>Patient Fetus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>30</td>
<td>First trimester*</td>
<td>8 (Unintentional)</td>
<td>Chemotherapy*</td>
<td>Resumed erlotinib postpartum</td>
<td>No signs of CMs</td>
</tr>
<tr>
<td>2*</td>
<td>Unknown</td>
<td>Fifth month</td>
<td>1 Dose, accidental</td>
<td>NA</td>
<td>NA</td>
<td>No signs of CMs</td>
</tr>
<tr>
<td>3*</td>
<td>Unknown</td>
<td>Fourth month</td>
<td>Pharmacist accidentally exposed (1 occurrence)</td>
<td>NA</td>
<td>NA</td>
<td>No signs of CMs</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>First trimester</td>
<td>Unknown</td>
<td>None</td>
<td>Proceeded to chemotherapy</td>
<td>Induced abortion</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>Unknown</td>
<td>A few doses</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Induced abortion</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>First trimester</td>
<td>8-12</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Induced abortion</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>First trimester</td>
<td>&lt;4</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Induced abortion</td>
</tr>
<tr>
<td>8*</td>
<td>40</td>
<td>First trimester*</td>
<td>33</td>
<td>None</td>
<td>Resumed erlotinib postpartum</td>
<td>Oligohydramnios and IUGR; No signs of CMs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(twin 1; higher exposure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>Second and third trimesters</td>
<td>18.5</td>
<td>Stereotactic radiation for brain metastases</td>
<td>Resumed erlotinib 3 wk postpartum and stereotactic radiation on primary lesion 2 mo after delivery</td>
<td>Velamentous placental cord insertion; IUGR; increased aspartate transaminase (almost resolved at 5 mo)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(twin 2; lower exposure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>Second and third trimesters</td>
<td>18.5</td>
<td>Stereotactic radiation for brain metastases</td>
<td>Resumed erlotinib 3 wk postpartum and stereotactic radiation on primary lesion 2 mo after delivery</td>
<td>1 Focus of avascular villi in the placental disc; increased aspartate transaminase level (resolved within 2 mo)*</td>
</tr>
</tbody>
</table>

Abbreviations: CM, congenital malformation; IUGR, intrauterine growth restriction; NA, not applicable.

* Eight patients with known pregnancy outcome and these 2 cases.
* Became pregnant while receiving treatment.

* Six cycles of cisplatin, gemcitabine, plus bisphosphonates prior to pregnancy.
* Pregnant, no cancer.
* See the Figure.
COMMENT & RESPONSE

Let Them Eat Fish

To the Editor Evidence presented by Daenen et al1 cannot be used to make dietary recommendations for humans regarding intake of fish oils, sources of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Dietary recommendations can be made only in the context of an adequate understanding of human nutrient requirements, dietary intakes, food composition, and nutrient metabolism. Dietary recommendations are developed by national agencies on the basis of rigid prespecified standards of evaluation of available evidence. There are currently no formal recommendations for fish oil intake as such, but recommendations for intake of n-3 fatty acids, α-linolenic acid [18:3(n-3)], and EPA+DHA among the healthy population are defined in some countries and regions. Rodent data are not a basis for determining human nutrient requirements or dietary recommendations.

The relevance of 16:4(n-3) (hexadec-4,7,10,13-tetraenoic acid) to human health is overstated by the authors,1 who refer to fish oil supplements or plasma as containing “relevant,” “elevated,” and “very high” levels of 16:4(n-3). The highest level of 16:4(n-3) found in any of the fish oil supplements tested is equivalent to 2 × 10^{-7} percent of total plasma fatty acids. These amounts would not be expected to be of consequence to human health.

High levels of fish intake are typical in certain countries (such as Japan), and no evidence exists for chemotherapy resistance in these countries.

Murphy et al2 reported that clinical benefit improved from 36% to 80% in patients with lung cancer who consumed fish oil (providing 2.2 g of EPA per day) throughout platinum-based doublet therapy (6 to 16 weeks). A clinical study providing DHA alone to women with advanced breast cancer reported median overall survival to be extended from 18 to 36 months.3 Several other benefits of fish oil ingestion have been reported during active cancer treatment.4,5 The wealth of literature derived from preclinical models supports the clinical studies and suggests that fatty acids found in fish oils improve the therapeutic index of multiple chemotherapies by increasing their efficacy, reducing their toxicity, or both; however, none of this literature was discussed by Daenen et al.1

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Conflict of Interest Disclosures: None reported.


To the Editor Daenen et al “advise patients to temporarily avoid fish oil” and also to “avoid herring and mackerel in the 48 hours surrounding chemotherapy exposure.”

Dietary recommendations, standards, and regulations are in the purview of regulatory agencies (eg, Food and Drug Administration, Health Canada). These organizations define nutrition-related health policies for the specific nutrients that are essential for the maintenance of growth, development, and health; they also define the upper safe limits of foods, nutrients, and food contaminants (eg, mercury in wild fish). There are high standards of evidence for the evaluation of health claims related to diet and for setting recommendations that form nutrition-related health policy. Regulatory authorities convene expert panels and base their decisions on the entire body of evidence relevant to the question or claim, and the quality and rigor of the methods used to obtain said evidence are critically reviewed.

Search on the terms fish oil, n-3 fatty acids, and cancer brings up several hundred articles. It is not imaginable that the authors of every individual research study would prologate a nutrition health claim related to their findings. This would serve no end but to strew confusion among patients and clinicians alike as to the potential benefits and risks, if any. A few experimental studies examined the interaction between antineoplastic therapy and n-3 polyunsaturated fatty acids (n-3PUFAs) derived from the oil of fatty marine fish. The findings show no consistent theme—there are suggestions that certain individual n-3 PUFAs sensitize tumors to chemotherapy and may reverse chemoresistance,2,3 as well as others suggesting the opposite.1,4 As Daenen et al5 concede in the Discussion of their article, there are no clinical data to support their advice. It is reassuring that standard chemotherapy has not been noted to lack efficacy in countries such as Japan, Greenland, or Norway, where fatty marine fish is a staple in the diet and typical daily intakes are well in excess of the amounts that Daenen et al5 claim to induce chemoresistance.