Taxanes for breast cancer during pregnancy: a systematic review

The co-occurrence of breast cancer and pregnancy is an important issue for the forthcoming years, given the trend for women to postpone childbearing [1]. Although the use of doxorubicin- and epirubicin-based regimens appear quite safe in the second and third trimesters of pregnancy [2, 3], little is known on the safety of taxanes, with only 14 cases found in our literature review 2 years ago [1].

We aimed to collect updated data on the safety of taxanes in pregnant patients, and therefore carried out a systematic review of the English literature by search of Pubmed, Embase, and Web of Knowledge, using the search terms ‘paclitaxel AND pregnancy’, ‘docetaxel AND pregnancy’, and ‘taxanes AND pregnancy’. Only papers published in English from 1990 to 15 September 2009 were included.

Twenty-three publications were identified [1, 4–12], describing 40 women and 42 neonates (two gemellar pregnancies). Paclitaxel was administered in 21 cases, docetaxel in 16 cases, and both drugs in 3 cases. Except for two cases [11, 13], taxanes were administered concomitantly or sequentially with other cytotoxic agents, mostly anthracyclines, cyclophosphamide, and platinum derivatives. Twenty-seven patients had breast cancer, 10 had ovarian cancer, and 3 had non-small-cell lung cancer. The 40 cases are summarized in Table 1. Docetaxel was administered during the first trimester.

Table 1. Clinical experience with taxanes during pregnancy (N = 40)

<table>
<thead>
<tr>
<th>Paclitaxel</th>
<th>Docetaxel</th>
<th>Paclitaxel + docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Maternal age at initiation of taxanes, years: median (range)</td>
<td>36 (30–42)</td>
<td>34 (26–44)</td>
</tr>
<tr>
<td>Gestational age at initiation of taxanes: n (T1/T2/T3)</td>
<td>0/17/4</td>
<td>2/10/4</td>
</tr>
<tr>
<td>Cumulative dose received during pregnancy, mg/m²: median (range)</td>
<td>550 (300–1620)</td>
<td>300 (175–570)</td>
</tr>
<tr>
<td>Toxicity during pregnancy (n)</td>
<td>Grade 1 nausea (2); grade 2 neutropenia (1); alopecia (2); hyperbilirubinemia (2); IUGR (1); preeclampsia (1); anhydramnios* (1)</td>
<td>Anhydramnios (1); hand–foot syndrome (1); preeclampsia (1)</td>
</tr>
<tr>
<td>Gestational age at delivery, weeks: median (range)</td>
<td>36 (30–38)</td>
<td>35 (32–40)</td>
</tr>
<tr>
<td>Type of delivery: n (vaginal/ C-section/NR)</td>
<td>2/11/8</td>
<td>5/7/4</td>
</tr>
<tr>
<td>Neonatal gender: n (Male/ Female/NR)</td>
<td>6/3/12</td>
<td>8/3/5</td>
</tr>
<tr>
<td>Neonatal birth weight, g: median (range)</td>
<td>2428 (1460–2800), n = 12</td>
<td>2245 (1490–3200), n = 9</td>
</tr>
<tr>
<td>Neonatal abnormalities (n)</td>
<td>Anemia (1), grade NR</td>
<td>Ventriculomegaly<em>a not related to docetaxel (2); holoprosencephaly suspected at birth</em>b (1)</td>
</tr>
<tr>
<td>Neonatal follow-up, months: median (range)</td>
<td>18 (9–36)</td>
<td>0 (0–2)</td>
</tr>
</tbody>
</table>

*Anhydramnios probably related to the concomitant treatment with trastuzumab.

†In both cases, ventriculomegaly was diagnosed before the initiation of docetaxel.

‡Considered normal at 32 months of follow-up.

NR, not reported; T1, first trimester; T2, second trimester; T3, third trimester; IUGR, intrauterine growth restriction; C-section, caesarean section.

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in 2 cases, whereas taxanes were started in the second and third trimesters in 30 and 8 cases, respectively.

Neither spontaneous abortions nor intrauterine deaths were reported. Maternal toxicity and neonatal status (Apgar scores and neonatal complete blood cell count) were poorly described. Basically, the maternal toxicity of both drugs appeared mild and manageable (Table 1). The use of granulocyte colony-stimulating factor was mentioned in one report, whereas the antiemetic regimen was never described. One neonate with various malformations including ventriculomegaly (diagnosed before the initiation of docetaxel) died at day 5 [12]. In two cases exposed to paclitaxel [7, 14], neonates born at 30 and 32 weeks developed acute respiratory distress possibly related to prematurity, requiring neonatal intensive care. The only malformation possibly related to taxanes is a case of pyloric stenosis in a neonate whose mother had received multiagent chemotherapy (doxorubicin, cyclophosphamide, paclitaxel, and docetaxel) [5].

Although the use of taxanes appeared feasible during the second and third trimesters of pregnancy, with a toxicity profile favorably compared with that of doxorubicin- and epirubicin-based regimens, such results should be interpreted cautiously given the methodological bias associated with the collection of data.

Taxanes are substrates for the P-glycoprotein (Pgp/MDR1/ABCB1), which is highly expressed on the maternal compartment of the placenta [1]. The Pgp protects the fetus against xenobiotics and might therefore reduce the transplacental transfer of taxanes. Moreover, doxetaxel and in a lesser extent paclitaxel are metabolized by cytochrome P-450 (CYP) 3A4. The activity of CYP3A4 is increased by 50%–100% during the third trimester of pregnancy [15], possibly resulting in a shorter half-life and a higher clearance of taxanes that could explain their toxicokinetic alterations. Nevertheless, these pharmacokinetic findings indicate that the efficacy of taxanes could be limited given the pregnancy-induced pharmacokinetic alterations.

In conclusion, this review of the literature evidenced a favorable toxicity profile of taxanes during the second and third trimesters of pregnancy, supported by pharmacological evidence. Additional clinical and pharmacokinetic reports on the use of taxanes during pregnancy, as well as studies assessing their transplacental transfer are required in order to confirm this safety profile and to better handle these drugs in pregnant cancer patients.

O. Mir1,2,3,*, P. Berveiller3, F. Goffinet4, J.-M. Treluyer2,3, R. Serreau3, F. Goldwasser1,5 and R. Rouzier3,5

1Department of Medical Oncology, Teaching Hospital Cochin, 2Department of Clinical Pharmacology, Clinical Research Unit, Teaching Hospital Cochin, Assistance Publique—Hôpitaux de Paris, University Paris Descartes, 3CALG Group: French Group of ‘Cancers Associés à La Grossesse’, 4Department of Gynecology and Obstetrics, Teaching Hospital Cochin, Assistance Publique—Hôpitaux de Paris, University Paris Descartes, 5Department of Gynecology and Obstetrics, Teaching Hospital Tenon, Assistance Publique—Hôpitaux de Paris, University Pierre et Marie Curie, Paris, France

(*E-mail: olivier.mir@ch.aph.fr)

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