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Controversy

Chemotherapy, targeted agents, antiemetics and growth-factors in human milk: How should we counsel cancer patients about breastfeeding?

Barbara Pistilli a, f, Giulia Bellettini b, Elisa Giovannetti c, Giovanni Codacci-Pisanelli d, Hatem A. Azim Jr. e, Giovanni Benedetti f, Maria Anna Sarno a, Fedro A. Peccatori a, *

a Fertility and Procreation in Oncology Unit, Department of Medicine, European Institute of Oncology, Milan, Italy
b Pediatrician International Board Certified Lactation Consultant, Milan, Italy
c Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands
d Division of Medical Oncology, Department of Medical and Surgical Sciences and Biotechnology, University of Rome “La Sapienza”, Roma, Italy
e Breast Cancer Translational Research Laboratory – J.C Heuson, Université Libre de Bruxelles Institut Jules Bordet, Brussels, Belgium
f Division of Medical Oncology, Ospedale di Macerata, Macerata, Italy

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abstract

An increasing number of women are diagnosed with cancer during pregnancy and lactation. Women are usually advised to interrupt breastfeeding during systemic anticancer treatment for fear of serious adverse effects to the nursed infant. However, the issue is poorly addressed in the literature and very few studies have evaluated the safety of breastfeeding during or after cytotoxic drugs or target agents administration. In this review we will analyze the available evidence that addresses the issue of anticancer drugs, targeted agents, antiemetics and growth-factors excretion in human milk. This could serve as a unique resource that may aid physicians in the management of breastfeeding cancer patients interested in maintaining lactation during treatment.

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Introduction

The rising incidence of pregnancies in older age has increased the probability that lactating women could be diagnosed with cancer. However, very limited data is available on breastfeeding during or after cancer diagnosis and treatment. Women are usually advised to interrupt breastfeeding during cytotoxic drugs administration, because of concerns of potentially serious side effects to the nursed infant. However, many of these restrictions depend on theoretical considerations rather than on clinical or pharmacological evidences. Breastfeeding mothers are excluded by nearly all clinical trials involving chemotherapy administration and current evidence on the safety of breastfeeding in these patients only rely on anecdotal case reports or small series.

The positive influence of breastfeeding on infant health and cognitive development is well established. Breastfeeding is an essential physiologic process that provides nutrition and protects the child against infection and immunologic disorders. 1, 2 It has been demonstrated that human milk contains different types of bioactive agents, which promote the development of newborn's host defense and the maturation of gastrointestinal tract, conferring long-term benefits to the infant. 3 Moreover, a large meta-analysis showed a reduced risk of testicular, gastric and premenopausal breast cancer in adult offspring who had been breastfed. 4, 6 On the other hand, breastfeeding mothers have a lower risk of developing breast and ovarian cancer with a significantly stronger protective effect associated with lactation for longer periods. 7, 8

Hence, given the important advantages of breastfeeding, it may occur that women diagnosed with cancer during pregnancy or lactation seek advice regarding the safety of breastfeeding during and after treatment. For a number of nursing mothers who have been recently diagnosed with cancer, stopping breastfeeding may carry additional emotional distress to the already heavy psychological burden of cancer diagnosis. 9 In the era of shared decision making, having data on cancer drug distribution in human milk may thus be helpful for more effective counseling and better treatment.
In this review we will consider published reports describing cases in which maternal plasma and breast milk had been collected for drug assays. Cancer patients usually receive other drugs that may pass into milk and could endanger the health of the baby, but we will focus on chemotherapy, targeted agents, including hormonal treatments, antiemetics and growth factors.

Factors governing drug passage into breast milk

It is generally known that the excretion of drugs into milk depends upon several factors, which include lipid solubility, molecular size, ionization, concentration and half-life in maternal plasma, protein binding and breastfeeding phase. The maternal plasma level of each specific drug is the most important factor determining the amount of medication transferred into breast milk. However, the high lipid solubility and low molecular weight of the drug may favor its passage to breast milk by simple diffusion and independently from concentration. Large molecules with high molecular-weight (> 600 Daltons), such as heparin and monoclonal antibodies hardly penetrate into human milk. Drugs with high albumin-bound fraction are invariably less concentrated in human milk compared to drugs with a high free plasma fraction, while the relatively low pH of human milk (7.0–7.2) favors the accumulation of weakly basic drugs. Finally, drug passage into the human milk is not constant across the different phases of breastfeeding. Plasma to milk transfer is highest during the first week of breastfeeding due to the presence of larger gaps between the alveolar breast cells, and the same might be true during the last part of breastfeeding, when glandular involution occurs and milk amount decreases. Large molecules that are usually segregated into mother’s plasma may thus be found in milk during these phases.

When counseling breastfeeding mothers who are under pharmacologic treatment, other factors are also important. Once the drug is present into the milk, the infant’s risk of toxicity is strictly dependent on absorbed milk volume, oral bioavailability of the drug and neonatal pharmacodynamics. Some drugs may have a local effect in the infant’s gastrointestinal tract and this should also be considered. Even if for many drugs the relative amounts sequestered into milk may be estimated, the gold standard for maternal counseling remains direct sampling and pharmacokinetics measurement of the drug of interest and its metabolites in maternal plasma and milk. Variations in individual metabolism may be particularly relevant in cancer patients where impairment in renal and hepatic function are common.

Chemotherapy

Breastfeeding is usually contraindicated in patients undergoing treatment with cytotoxic agents for fear of potential infant genotoxicity. However, scanty evidences support this recommendation, since milk concentration of chemotherapeutic drugs has been assessed in only few case-reports (Table 1).

Cisplatin passage in human milk remains controversial. One case report demonstrated undetectable (<0.1 μg/ml) milk platinum levels after 100 mg/m² of cisplatin administered for an advanced ovarian cancer. Another paper reported considerable high levels reaching 900 μg/L after the second daily dose of cisplatin 20 mg/m². Ben-Baruch and colleagues assessed milk platinum levels in a patient treated with cisplatin 60 mg/m² collecting samples from two cycles. They found average milk platinum concentration of 125 μg/L at 30 min after the first dose and 112 μg/L at 18 h, corresponding to 10% of simultaneous plasma levels over the 18-h sampling period. More recently, a series of breast milk samples were collected from three out of eight patients receiving weekly cisplatin 20 mg/m² during pregnancy as neoadjuvant chemotherapy for gestational cervical cancer. Breast milk samples were taken during the first day of lactation. Cisplatin concentrations in milk were reported to be 0.2, 1.4 and 5.5 μg/L, which correspond respectively 0.9%, 2.3% and 9% of maternal blood concentrations. Considering these observations, we believe that breastfeeding should be discouraged in patients undergoing treatment with cisplatin.

Methotrexate milk concentration was assessed for 12 consecutive days in one breastfeeding woman with chorioncarcinoma receiving an oral dose of 22.5 mg/day. A peak milk level of 2.3 μg/L occurred 10 h after drug administration followed by a subsequent dropping, with a milk/plasma ratio of 0.08. Six milk samples were also obtained from a woman treated with a single intramuscular dose of 65 mg of methotrexate for ectopic pregnancy. Over a 24-hcollecting time, methotrexate was undetectable in all milk samples. Accordingly, in patients treated with low dose regimens of methotrexate for arthritis (up to 65 mg), breastfeeding has been deemed safe by some authors, but not all agree. Nonetheless, extreme caution should be exercised when higher doses are required as for cancer treatment. In this case methotrexate passage into milk is likely to occur and potential adverse effects in the breastfed infant may not be completely excluded. Methotrexate is moderately absorbed (33%) orally and may cause gut inflammation in the infant, thus is probably safer to discard milk for at least a week after its administration in oncological patients.

High milk levels of doxorubicin and its active metabolite doxorubicinol were detectable in milk for at least 72 h, according to the findings by Egan and colleagues. After intravenous administration of 70 mg/m² of doxorubicin in association with cisplatin to a lactating patient with ovarian cancer, they found significant milk levels of doxorubicin and doxorubicinol at 24 h (128 and 111 μg/L, respectively). Maximum milk concentration of doxorubicin was 4.4 times higher than those detected in concomitant plasma samples and the AUC of doxorubicinol was 10 times higher in milk compared to plasma. Based on these data, the infant would have received an estimated 2% of maternal weight-adjusted dosage if...
he had been nursed throughout the 72 h after chemotherapy administration. According to these findings, breastfeeding should be avoided in patients undergoing treatment with doxorubicin.

Human milk levels of etoposide and mitoxantrone were assessed in a nursing woman who received combination chemotherapy for acute promyelocytic leukemia. The patient was exposed to daily intravenous mitoxantrone 6 mg/m² for 3 days, daily intravenous etoposide 80 mg/m² for 5 days and intravenous cytarabine 170 mg/m². Etoposide milk concentration reached a peak of about 800 mg/L after the 3rd dose, and then dramatically dropped until it was undetectable in milk after 24 h. Conversely, a very slow clearance of mitoxantrone was demonstrated. Its level smoothly decreased to a plateau value of 20 μg/L by 7 days and remained at 18 μg/L at 28 days after the last dose. From this single report, no firm conclusions can be drawn. However, it seems reasonable to withhold breastfeeding while on treatment with mitoxantrone, and to wait at least 72 h after etoposide administration.

Recently, we investigated the pharmacokinetics of 5-fluorouracil (5-FU) in maternal milk and plasma samples from a breastfeeding woman diagnosed with locally advanced rectal cancer. A total of 33 milk samples were collected and tested over a 32-day period. Despite maternal plasma concentration of the drug ranging between 10.8 and 116.8 μM, 5-FU levels were undetectable in milk at any time during and after chemotherapy. We speculated that 5-FU excretion in milk was undetectable for various reasons: firstly, more than 80% of 5-FU is rapidly degraded into inactive metabolites by dihydropyrimidine dehydrogenase, with a mean half-life of elimination from plasma of approximately 16 min; secondly, limited lipid solubility of 5-FU along with the binding to plasma protein (8–12% of plasma concentration) also play an important role; finally, according to alveolar gaps dimension, it is likely that we did not detect plasma-to-milk 5-FU excretion, because we analyzed mature milk. Our findings also demonstrated that the daily amount of milk was not reduced by 5-FU continuous infusion.

Even if data are scarce, chemotherapy is unlikely to have short or long-term effect on milk production. If the milk production is maintained during treatment by regular breast pumping, breastfeeding can nearly always be recovered immediately after the end of treatment. In patients who have had anticancer chemotherapy long before the onset of a subsequent pregnancy, lactation is usually feasible. In breast cancer patients who received adjuvant chemotherapy with antracyclines, alkylating agents and taxanes, milk production was normal and even increased from the unaffected breast, provided concerns regarding abnormal growth of the peripheral microvasculature and nervous system, owing to platelet derived growth factor receptor β (PDGFRβ) inhibition. Similiar results were obtained in breast milk samples collected over 2 months from another CML patient who had been breastfeeding her son during the administration of imatinib at the dosage of 400 mg/day. Imatinib and GCP74588 showed relatively high concentrations in milk, with milk-plasma ratio of 0.5 and 0.9 respectively. However, considering the maximum daily milk intake of 777 ml, the infant would have received not more than 3 mg/day of imatinib and GCP74588, a dose quite far from therapeutic ranges. Similar results were reported in the third case, where imatinib was detected in several milk samples collected on different postpartum days (Table 2).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Drugs</th>
<th>Number of patients</th>
<th>Dose administered</th>
<th>Milk excretion</th>
<th>Time of detection since drug administration</th>
<th>Milk sampling period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russell et al.</td>
<td>Imatinib</td>
<td>1</td>
<td>400 mg/day</td>
<td>596 ng/ml (imatinib) 1513 ng/ml (GCP74588) milk-plasma ratio: 0.5 (imatinib) 0.9 (GCP74588)</td>
<td>15 h</td>
<td>Single detection</td>
</tr>
<tr>
<td>Gambacorti-Passerini et al.</td>
<td>Imatinib</td>
<td>1</td>
<td>400 mg/day</td>
<td>1, 2, 3, 4, 9 h</td>
<td>2 Months</td>
<td></td>
</tr>
</tbody>
</table>

Note: h, hours.

In recent years, a rising number of monoclonal antibodies and tyrosine-kinase inhibitors have been incorporated in the management of several tumors. However, the short period of clinical experience limits our knowledge regarding the safety of targeted agents in breastfeeding patients.

Even if more than 200 cases of imatinib exposure during pregnancy were reported, very few of them focused on the potential exposure of the infant to imatinib through breastfeeding. Breast milk was collected and evaluated in three pregnant patients with chronic myeloid leukemia (CML) treated with imatinib 400 mg/day. In the first report, authors assessed imatinib and its active metabolite GCP74588 concentrations in maternal blood, placenta, umbilical cord blood and breast milk. High concentration of imatinib and GCP74588 were detected in a single sample of breast milk collected 7 days postpartum, 15 h after a 400 mg oral dose of imatinib (596 ng/ml and 1513 ng/ml, respectively). Although an infant consuming 600–1000 ml of milk daily would ingest only 1.2–2.0 mg of both molecules, the authors concluded that breastfeeding should be avoided while on imatinib, because of theoretical concerns regarding abnormal growth of the peripheral microvasculature and nervous system, owing to platelet derived growth factor receptor β (PDGFRβ) inhibition. Similar results were obtained in breast milk samples collected over 2 months from another CML patient who had been breastfeeding her son during the administration of imatinib at the dosage of 400 mg/day. Imatinib and GCP74588 showed relatively high concentrations in milk, with milk-plasma ratio of 0.5 and 0.9 respectively. However, considering the maximum daily milk intake of 777 ml, the infant would have received not more than 3 mg/day of imatinib and GCP74588, a dose quite far from therapeutic ranges. Similar results were reported in the third case, where imatinib was detected in several milk samples collected on different postpartum days (Table 2).

No evidence is available on the excretion of sunitinib into human milk. Animal reproductive studies have shown that sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12 times higher than in plasma.

It is noteworthy that there are no data on the excretion of trastuzumab, rituximab and cetuximab into human milk, although they have been increasingly employed in clinical practice. In the last
decade, trastuzumab and rituximab are the only monoclonal antibodiess administered to pregnant cancer patients, but no data are available on breastfeeding. 37 Similarly, no data were reported on the excretion of bevacizumab into human milk following systemic administration. Only one case of intravitreal injections during breastfeeding was described. The authors did not report any side effects in the breastfed infant but no pharmacokinetics studies were performed. 38 Since IgG are large molecules, they are not excreted in human milk, with the exception of the very first and very last days of lactation. 11 Thus breastfeeding is probably safe during their administration.

Fine modulo

Since tamoxifen has been largely used to suppress the production of milk, no evidence is available on its excretion into human milk. In two published clinical trials, tamoxifen demonstrated to be more effective than placebo in suppressing serum prolactin rise and in preventing lactation and breast engorgement in postpartum mothers. However, its concentration in milk was not assessed. 29,40

In summary, very few data are available on milk passage of targeted agents in human milk. Imatinib passes into the milk with a plasma/milk ratio of approximately 0.7 and even if the total daily amount assumed by the baby would be very low, concern remains about the potential detrimental effects of such a potent inhibitor of tyrosine kinase in a growing organism. The same holds true for tamoxifen or other selective estrogen receptor modulators, which probably pass into the milk and could be absorbed by the baby with untoward effects. Monoclonal antibodies, on the contrary, are probably safe during breastfeeding.

Antiemetics

Metoclopramide is widely used for reducing nausea and vomiting associated with mildly emetogenic chemotherapy regimens. It antagonizes the release of dopamine in the central nervous system and has pro-kinetic gastro intestinal effect. 41 Moreover, it stimulate prolactin release, thus increasing milk production. Metoclopramide concentration is greater in milk than in plasma, with an approximate 2/1 ratio. The peak milk concentration occurs 2–3 h after maternal administration and is higher during early puerperium. 42 The higher milk level is due to the ionization of the drug and to its lipophilic nature. 33,44 In one study, milk concentration of metoclopramide varied from 20 to 157 µg/L. 42 However, even with these milk levels, the average daily dose of metoclopramide taken by the breastfed infant would have been between 1 and 24 µg/kg/day, which is much lower than the recommended dose for gastro esophageal reflux in pediatric patients. Most authors have reported the absence of side effects in newborns whose mothers received metoclopramide to increase milk production.32–46

To date, no reports have evaluated the excretion of 5-HT3 receptor antagonists (ondansetron, granisetron, tropisetron) into human milk. Ondansetron and its metabolites have been found in the milk of lactating rats (product information 1997). In addition, owing to its relatively low molecular weight, excretion into human breast milk should be expected.

In summary, metoclopramide is the drug of choice among antiemetics and breastfeeding can be safely continued during its use.

Growth factors

The excretion of erythropoietin and darbepoetin in human breast milk has not been extensively studied. However, it should be safe because erythropoietin is a normal component of human milk and oral absorption of erythropoetin α and other recombinant forms of erythropoietin in infants appears to be limited. 47–49

Human milk contains significant levels of granulocyte colony-stimulating factor (G-CSF). Its concentration increases after intra amniotic injection and during the first 2 postpartum days. 50 Breast milk concentration of the recombinant G-CSF lenograstim was assessed in a nursing mother receiving lenograstim subcutaneously at increasing dosages (300–600 µg) in order to donate peripheral blood hematopoietic stem cells for allogeneic transplantation. Lenograstim milk levels increased during therapy up to 85.7 ng/L on day 6, corresponding to an infant dosage of about 0.013 µg/kg. 51 Similarly, milk concentrations of filgrastim were measured in a nursing woman who received filgrastim at increasing dosages (300–600 µg) for peripheral blood hematopoietic stem cells harvest. Filgrastim was detected in the milk at a dosage of 188 ng/L, 22 h after the first administration and slowly declined until was undetectable (<10 ng/L) 70 h after the last administration. 52 Because filgrastim is not orally absorbed, any quantity excreted into milk is unlikely to adversely affect the breastfed infant. 52

Conclusions

Most breastfeeding women are advised to interrupt nursing during cancer treatment, because of concerns of potentially serious side effects to the nursed infant. However, abrupt weaning can be psychologically traumatic for both mother and child and in some cases could be unnecessary. According to the biological and psychological value of breastfeeding, oncologists, hematologists and neonatologists should be aware of the safety of some drugs used in cancer management when given during breastfeeding.

5-fluorouracil and etoposide seem to be undetectable in maternal milk after 24 h from their administration. Similarly, there are a number of evidences about safety of metoclopramide and growth factors. On the contrary, doxorubicin, cisplatin, mitoxantrone and high-dose methotrexate should be avoided in breastfeeding patients due to their high plasma-milk passage. Few data on the milk excretion of targeted agents and hormonal therapy has been published and no definitive conclusion can be taken.

Collecting maternal plasma and breast milk for drug assays during and after cancer treatment is not impractical, as it may seem. Furthermore, the development of patient registries or surveillance programs for medications used during pregnancy and breastfeeding should give some guidance for physicians dealing with nursing cancer patients. Some work has been done, much more remains to be done.

Conflict of interest statement

All authors declare no conflict of interest.

References


