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Hot Topic

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

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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.

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.

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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.[10] 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 ($\geqslant$600 Daltons), such as heparin and monoclonal antibodies hardly penetrate into human milk.[11] 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.[12,13] 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 secreted 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.[14–16] 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/m^2 of cisplatin administered for an advanced ovarian cancer.[17] Another paper reported considerable high levels reaching 900 μg/L after the second daily dose of cisplatin 20 mg/m^2.[18] Ben-Baruch and colleagues assessed milk platinum levels in a patient treated with cisplatin 60 mg/m^2 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.[19] More recently, a series of breast milk samples were collected from three out of eight patients receiving weekly cisplatin 20 mg/m^2 during pregnancy as neoadjuvant chemotherapy for gestational cervical cancer.[20] 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 choriocarcinoma 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.[21] 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-h collecting time, methotrexate was undetectable in all milk samples.[22] 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.[14,23,24] 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.[14]

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/m^2 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

Table 1
Reported data on human milk excretion of chemotherapeutic drugs.

Drugs	Absolute drug concentration in milk (relative infant dose)	Safety	References
Cisplatin	0.2–900 μg/L (ND)	Conflicting reports. Avoidance of breastfeeding is advisable	Egan et al.[17], De Vries et al.[18], Ben-Baruch et al.[19], Lenowska et al.[20]
Methotrexate	2.3 μg/L (0.1%)	Exercise caution if high dose	Johns et al.[21]
Doxorubicin	128 μg/L (2%)	Avoidance of breastfeeding is advisable	Egan et al.[17]
Mitoxantrone	120 μg/L (ND)	Passage into milk and slow clearance. Breastfeeding should be avoided	Azuno et al.[25]
Etoposide	800 mg/L (ND)	Probably safe after 72 h since administration	Azuno et al.[25]
5-Fluorouracil	Undetectable	Probably safe	Peccatori et al.[16]

ND, no data available.