European Journal of Cancer 119 (2019) 107–111

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Letter to the Editor

Breastfeeding during R-CHOP chemotherapy: please abstain!

Giovanni Codacci-Pisanelli [a,*], Richard J. Honeywell [b], Natalie Asselin [c], Giulia Bellettini [d], Godefridus J. Peters [b], Elisa Giovannetti [b,e,1], Fedro A. Peccatori [f,1]

[a] *Dept. Medical and Surgical Sciences and Biotechnology, University of Rome "la Sapienza", Italy*
[b] *Laboratory Medical Oncology, VU University Medical Center, CCA 1.52, Amsterdam, the Netherlands*
[c] *Shediac, Canada*
[d] *ASST Milan, Milan, Italy*
[e] *Cancer Pharmacology Lab, AIRC Start-Up Unit, Pisa, Italy*
[f] *European Institute of Oncology IRCCS, Division of Gynecologic Oncology, Milan, Italy*

Received 28 June 2019; accepted 2 July 2019
Available online 19 August 2019

Treatment of cancer during pregnancy has been extensively studied, but few data are available about the management of women with cancer diagnosed during breastfeeding.

Breastfeeding offers many advantages to mothers and their children, but anticancer drugs may pass into human milk and damage infants [1,2], whose detoxifying systems are still in development [3]. Thus, knowledge about the excretion of anticancer drugs in breast milk is relevant, because in the absence of data most women stop breastfeeding while receiving (chemo)therapy. Here, we report the concentrations of antineoplastic drugs in the milk of a woman who maintained lactation with breast pumping during R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) therapy.

A 37-year-old Caucasian woman was diagnosed with stage IV diffuse large B-cell non-Hodgkin lymphoma at 4 months postpartum. The patient was breastfeeding her baby before diagnosis and searched for information regarding the safety of breastfeeding during treatment. Owing to the uncertainties about excretion of anticancer drugs in human milk, the patient stopped breastfeeding her daughter but proposed to regularly pump her milk and test the levels of drugs in the milk to increase knowledge of drug excretion for subsequent mothers in her condition.

She received R-CHOP (rituximab [375 mg/m^2], cyclophosphamide [750 mg/m^2], doxorubicin [50 mg/m^2], vincristine [1.4 mg/m^2 capped at 2 mg maximal total dose] plus prednisone [40 mg/m^2/day]) every 21 days for 6 cycles. She also received 300 mg of allopurinol orally during the whole therapy course.

Samples were collected twice daily during the first 3 courses of treatment, although milk production decreased significantly across this time period. During the remaining courses, only one sample per day was collected.

An electric breast pump was used to collect milk samples. A total of 290 samples were provided. All samples were transferred from the storage bags to

* *Corresponding author*: Corso della Repubblica, 79, 04100 Latina Italy. Fax: +390623317568.
E-mail address: Giovanni.Codacci-Pisanelli@uniroma1.it (G. Codacci-Pisanelli).
[1] Dr. Giovannetti and Dr. Peccatori share senior authorship.

https://doi.org/10.1016/j.ejca.2019.07.012

labelled 15-ml tubes and then stored in the freezer (−20 °C) until analysis.

Chromatography was conducted using a Dionex Ultimate 3000 system coupled with an Applied Biosciences SCIEX API 3000 mass spectrometer for drug detection, and standard calibration and extraction were performed, as described for similar cytostatics [4].

Extraction of drugs and analysis were based on previously published high-performance liquid chromatography-fluorescence and liquid chromatography (LC)–mass spectrometry (MS) methodology for tissues [5–9] adapted for simultaneous analysis by LC–MS (Fig. 1). Data analysis was performed using Chromeleon-6.7 chromatography data system software (Dionex, Munchen, Germany). Concentrations less than 1 ng/ml were neglected. Areas under the milk concentration–time curves were calculated using standard software, performing these analyses in parallel with analyses on human milk samples, generously given by a healthy donor spiked with different concentrations of the drugs.

We focused on the concentrations of doxorubicin, its primary metabolite doxorubicinol and cyclophosphamide. Doxorubicin and doxorubicinol were measurable at high concentrations in the milk of the patient after receiving R-CHOP. Metabolites of cyclophosphamide were also measurable in notable quantities, with the limit that reference standards were not available; thus, metabolite levels were estimated based on the linear regression of the parent compound. Vincristine was not detected in any of the samples tested, but the detection limit of the system was relatively high for vincristine; thus, the presence of low concentrations of vincristine into milk cannot be excluded.

Concentrations of the parent compounds doxorubicin and cyclophosphamide (Fig. 2A and B) rapidly reached a peak after R-CHOP administration and then decreased over time. The formation of the metabolite doxorubicinol was somewhat delayed (Fig. 2C), but it showed a progressive increase and reached a peak 10 times higher than that of the parent drug. Doxorubicinol was eliminated from the milk at a slower rate than the parent drug persisting at elevated levels until 10 days after infusion. Remarkably, doxorubicin, doxorubicinol and cyclophosphamide were still detectable at low levels 21 days after the first administration. A

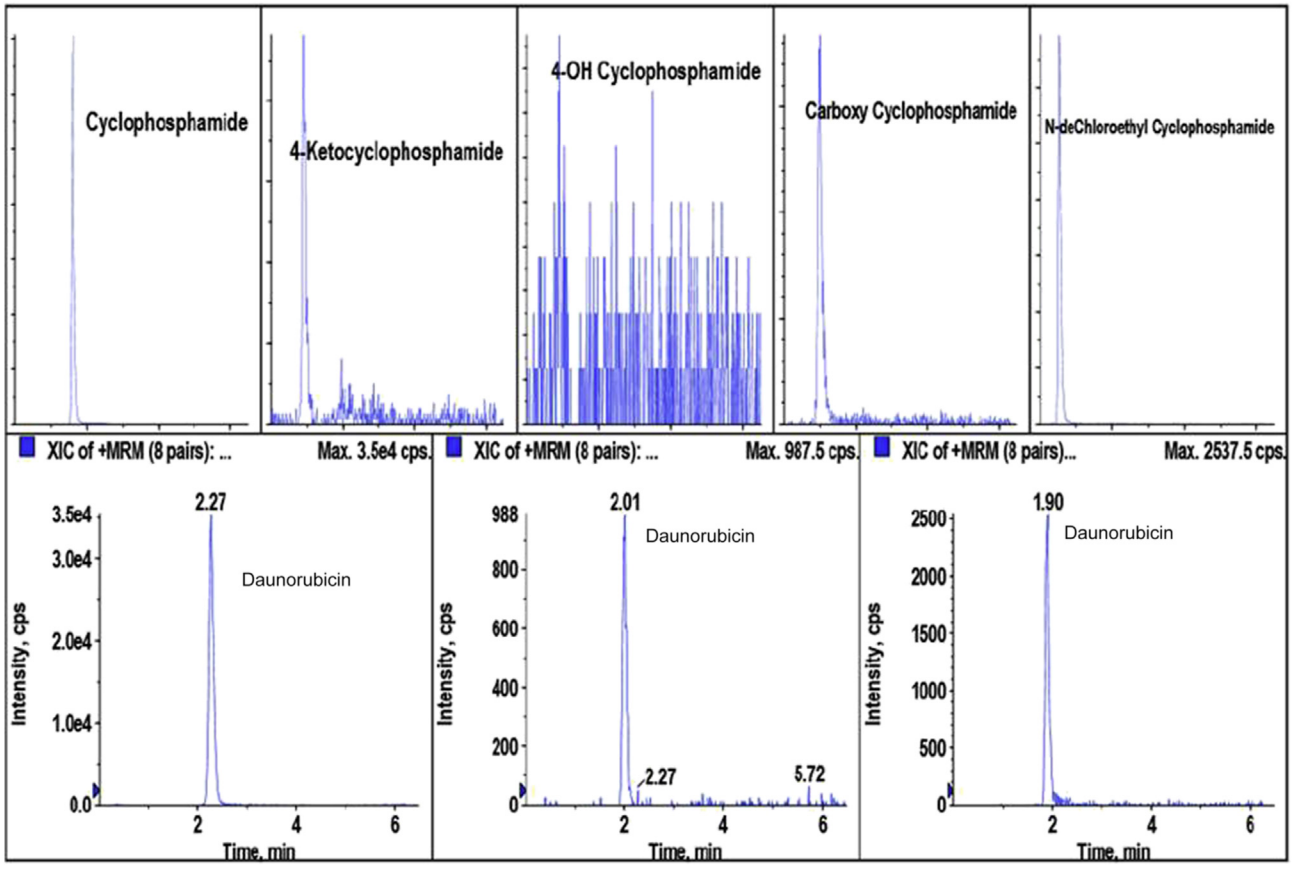

Fig. 1. Representative chromatograms of doxorubicin and cyclophosphamide and their metabolites in milk samples. Daunorubicin was used as an internal standard. The chromatograms of the metabolites of cyclophosphamide are based on fragmentation patterns based on LC–MS characteristics deducted from the structures and as published by Vredenburg *et al* [6]. However, exact quantification was not possible owing to the lack of purified metabolites. LC, liquid chromatography; MS, mass spectrometry.

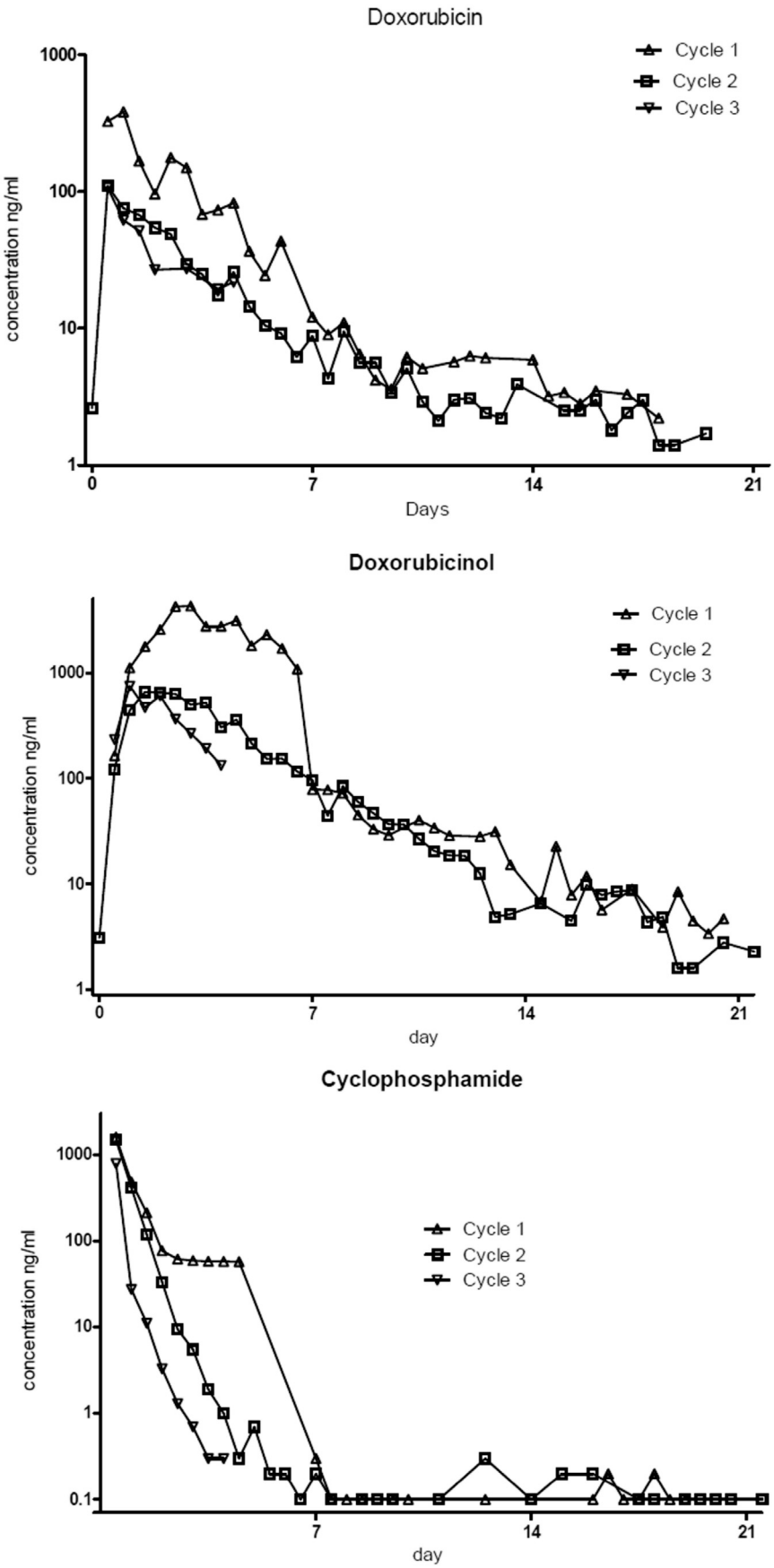

Fig. 2. Plots of the LC–MS–determined concentrations of milk doxorubicin (A), doxorubicinol (B) and cyclophosphamide (C) during 3 cycles of chemotherapy. LC, liquid chromatography; MS, mass spectrometry.

decrease in peak concentration was seen from the 1st to 2nd to 3rd course (See Fig. 2).

To our knowledge, this is the first report of a prolonged evaluation of doxorubicin, its metabolite doxorubicinol and cyclophosphamide and its metabolites in human milk. Oral absorption of anticancer drugs in adults is often limited, but this may be different for infants because the permeability of the gastrointestinal mucosa may be higher while metabolic enzymes may be less active [10].

The advantages of breastfeeding for the health of both infants and mothers include reduced infant mortality and morbidity, lower rates of childhood infections, obesity, diabetes and leukaemia and reduced rates of maternal premenopausal breast cancer, diabetes and osteoporosis. However, anticancer drugs administered to a lactating woman may pass into her milk [1] and subsequently may be taken up by the baby, with adverse effects according to the 'infant dose' [10]. Regrettably, only a limited amount of information is based on lactation-specific data, as reported in the LactMed database (https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm).

Measurable concentrations of cyclophosphamide (and several metabolites), doxorubicin and doxorubicinol were observed in milk for at least 21 days after administration. Doxorubicinol reached its peak in milk later than the parent drug, but its concentrations were 10-fold higher. Earlier, Egan *et al.* [7] demonstrated the presence of doxorubicin in milk up to 78 h after doxorubicin administration and concluded that a nursing child would only absorb a small amount of anthracyclines. However, because doxorubicinol is maintained at a high plateau until at least 7 days, it can be concluded that the infant will be exposed to the drug for a long period. It should therefore be advised not to breastfeed the child, which is in agreement with the recommendation of Egan *et al.* [7] to advise women receiving chemotherapy 'to refrain from breastfeeding their infants'.

Concerning cyclophosphamide, it was already shown that this drug not only passes into milk but also may cause toxic effects on the infant [9]. Our data show that (toxic) cyclophosphamide metabolites are being found extensively in breast milk, which are possibly responsible for these toxic effects.

Vincristine was not measurable in our samples, but low levels cannot be excluded. Our patient also received allopurinol, which could not be analysed by the applied assay. However, earlier, it was demonstrated that at a dose of 300 mg, both allopurinol and its active metabolite oxypurinol were found in breast milk but that only oxypurinol was found in the infant's plasma [11]. These authors did not observe any side-effects during 6 weeks of breastfeeding. We did not measure rituximab, but earlier data showed that excretion of IgG antibodies into milk is quite limited [12] and the oral absorption is negligible.

Our patient also received prednisone for 5 days per cycle as part of her treatment. Previous data suggest that the milk concentration of steroids is very low after a few hours after a relatively high oral dose and, therefore, is not considered a problem [13].

Owing to the prolonged persistence of doxorubicin, its metabolite doxorubicinol, cyclophosphamide and some metabolites in breast milk, breastfeeding should be discouraged for at least 6 weeks after treatment. For motivated mothers wishing to breastfeed their babies after R-CHOP treatment, regular breast pumping during therapy with milk discharge and subsequent resumption of breastfeeding after 6 weeks from the last doses may be a possible strategy, with the limits of the few data available.

Conflicts of interest

The authors declare that they have no conflict of interest, directly or indirectly connected to the present article, to declare.

Funding

This work was supported by the Cancer Center Amsterdam (the Netherlands), Italian Association for Cancer Research (AIRC/Start-Up grant, Italy), and KWF Dutch Cancer Society (KWF project 10401, the Netherlands)

Ethical aspects

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was obtained from our patient, and her privacy rights have been observed.

Role of the funding source

The funding organisations had no role in the performance of this study or in data analysis or interpretation.

Acknowledgements

The authors would like to express their admiration for the strength demonstrated by their patient who conceived and made this study possible. The authors are grateful to her, and they think all women who in the future may receive any benefit from this article should share their feeling.

References

[1] Pistilli B, Bellettini G, Giovannetti E, Codacci-Pisanelli G, Azim HA, Benedetti G, et al. Chemotherapy, targeted agents, antiemetics and growth-factors in human milk: how should we

counsel cancer patients about breastfeeding? Cancer Treat Rev 2013;39:207–11. https://doi.org/10.1016/j.ctrv.2012.10.002.
[2] Amato D, Niblett JS. Neutropenia from cyclophosphamide in breast milk. Med J Aust 1977;1:383–4.
[3] Hotham N, Hotham E. Drugs in breastfeeding. Aust Prescr 2015; 38:156–9. https://doi.org/10.18773/austprescr.2015.056.
[4] Adema AD, van der Born K, Honeywell RJ, Peters GJ. Cell cycle effects and increased adduct formation by temozolomide enhance the effect of cytotoxic and targeted agents in lung cancer cell lines. J Chemother 2009;21:338–46. https://doi.org/10.1179/joc.2009.21.3.338.
[5] de Jong J, Guérand WS, Schoofs PR, Bast A, van der Vijgh WJ. Simple and sensitive quantification of anthracyclines in mouse atrial tissue using high-performance liquid chromatography and fluorescence detection. J Chromatogr 1991;570:209–16.
[6] Vredenburg G, den Braver-Sewradj S, van Vugt-Lussenburg BMA, Vermeulen NPE, Commandeur JNM, Vos JC. Activation of the anticancer drugs cyclophosphamide and ifosfamide by cytochrome P450 BM3 mutants. Toxicol Lett 2015;232: 182–92. https://doi.org/10.1016/j.toxlet.2014.11.005.
[7] Egan PC, Costanza ME, Dodion P, Egorin MJ, Bachur NR. Doxorubicin and cisplatin excretion into human milk. Cancer Treat Rep 1985;69:1387–9.
[8] Atkinson HC, Begg EJ, Darlow BA. Drugs in human milk. Clinical pharmacokinetic considerations. Clin Pharmacokinet 1988;14:217–40. https://doi.org/10.2165/00003088-198814040-00003.
[9] Wiernik PH, Duncan JH. Cyclophosphamide in human milk. Lancet (London, England) 1971;1:912.
[10] Begg EJ, Duffull SB, Hackett LP, Ilett KF. Studying drugs in human milk: time to unify the approach. J Hum Lactation 2002; 18:323–32. https://doi.org/10.1177/089033402237904.
[11] Kamilli I, Gresser U. Allopurinol and oxypurinol in human breast milk. Clin Investig 1993;71:161–4.
[12] Bragnes Y, Boshuizen R, de Vries A, Å Lexberg, Østensen M. Low level of Rituximab in human breast milk in a patient treated during lactation. Rheumatology 2017;56:1047–8. https://doi.org/10.1093/rheumatology/kex039.
[13] Ost L, Wettrell G, Björkhem I, Rane A. Prednisolone excretion in human milk. J Pediatr 1985;106:1008–11.