''The only thing I know is that I know nothing'': 5-fluorouracil in human milk

Women are usually advised to interrupt breastfeeding during chemotherapy for concerns of serious side-effects to the infant. However, the passage of cytotoxic drugs in human milk has been poorly studied.

A 36-year-old woman was diagnosed with rectal cancer while she was still breastfeeding her 9-month-old son. The tumor was staged as cT3N1M0 and neoadjuvant 5-flourouracil (5-FU)-based chemoradiotherapy (CRT) was planned. She was advised to stop nursing, however, she expressed her desire to resume breastfeeding after treatment.

After a multidisciplinary discussion, the patient was advised to pump her breasts twice daily during CRT in order to maintain milk production. To decide when breastfeeding could be safely resumed, we evaluated the pharmacokinetics of 5-FU in milk.

The patient received standard CRT with 5-FU 200 mg/m^2/day as i.v. continuous infusion concurrently with pelvic radiotherapy. Samples of peripheral blood were taken before the start of 5-FU and after 1, 2 and 5 weeks. Milk samples were obtained before, during and up to 10 days following the completion of therapy.

5-FU concentrations were measured using an high-performance liquid chromatography (HPLC) method [1] modified and optimized for plasma and milk samples. Four plasma samples were collected and analyzed. The concentration of 5-FU in plasma ranged between 11.14 and 114.95 μM (Figure 1A and B). Thirty-three milk samples were collected and tested. 5-FU levels were undetectable in milk at any time during and after CRT treatment. To validate the HPLC methodology used, we carried out parallel analyses on human milk spiked with different concentrations of 5-FU, which were stored, extracted and measured in the same conditions. 5-FU was detected in the validation samples with a limit of detection at 0.5 μM (Figure1C and D).

The patient completed the planned treatment and eventually underwent radical surgery without complications. Ten days after surgery, when pharmacokinetics results were available, the patient tried to resume breastfeeding, but her infant refused to latch.

Breastfeeding is an essential physiologic process that provides nutrition and protects the child against infection, immunologic disorders and some types of cancer during adulthood [2, 3]. Nevertheless and despite the lack of evidence, breastfeeding is usually not recommended during maternal chemotherapy because of the potential toxic effects to the infant.

In this case, we report for the first time that 5-FU was undetectable at any time during and following CRT, although maternal plasma concentrations reflected normal pharmacokinetics. The amount of a drug or its metabolites excreted into milk is dependent upon several factors: lipid solubility, molecular size, ionization, protein binding and half-life in maternal plasma [4]. 5-FU has a short half-life and a high protein bound in serum [5]; these factors probably accounted for the undetectable levels of 5-FU in milk.

Our results are reassuring, but genetic background and plasma levels variability might influence 5-FU distribution into milk. Collecting breast milk for drug assays during and after chemotherapy, as impractical as this approach may seem, could provide valuable information to counsel patients receiving chemotherapy who are willing to resume breastfeeding after the end of treatment.

F. A. Peccatori[1]*, E. Giovannetti[2], B. Pistilli[1,3], G. Bellettini[4], G. Codacci-Pisanelli[5], N. Losekoot[2], G. Curigliano[6], H. A. Azim Jr[7], A. Goldhirsch[6] & G. J. Peters[2]

[1]Fertility and Procreation in Oncology Unit, Department of Medicine, European Institute of Oncology, Milan, Italy, [2]Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands, [3]Department of Medical Oncology, Ospedale di Macerata, Macerata, [4]Pediatrician International Board Certified Lactation Consultant, Milan, [5]Division of Medical Oncology, Department of Medical and Surgical

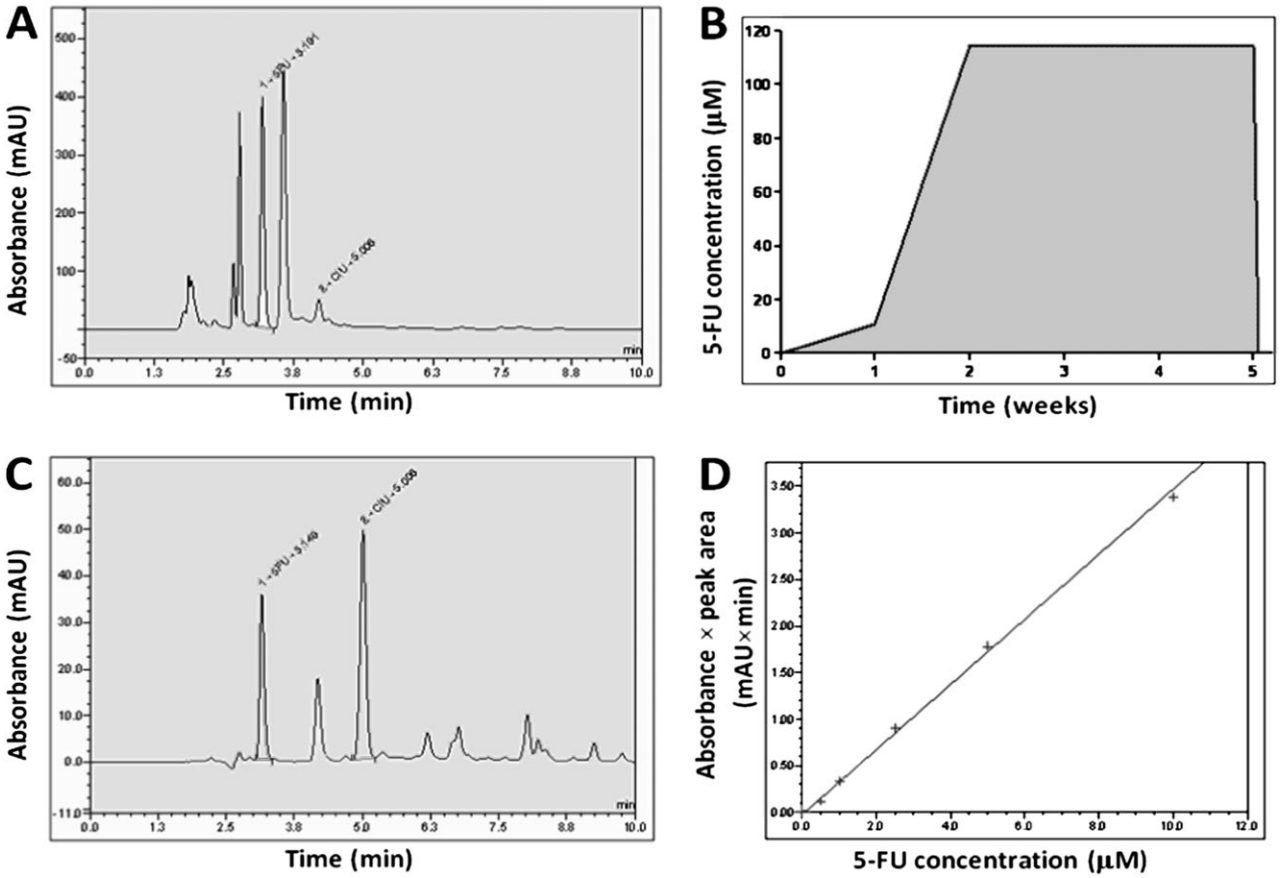

Figure 1. HPLC assay for 5-fluorouracil (5-FU). (A) Representative HPLC-UV chromatograph of 5-FU and chlorouracil (CIU, used as internal standard) profiles in a plasma sample (note: the numbers near the 5-FU and CIU peaks refer to their specific retention times). (B) Plot of the HPLC-determined concentration of plasma 5-FU. (C) Representative HPLC-UV chromatograph of 5-FU and CIU (used as internal standard) profiles in 5-FU-spiked milk samples from a healthy donor. (D) Calibration curve of 5-FU (0.5, 1, 2.5, 5 and 10 μM) obtained in 5-FU-spiked milk from a healthy donor.

Sciences and Biotechnology, University of Rome "La Sapienza", Rome, [6]Medical Oncology Division, Department of Medicine, European Institute of Oncology, Milan, Italy, [7]Breast Cancer Translational Research Laboratory J.C. Heuson, Université Libre de Bruxelles, Institut Jules Bordet, Brussels, Belgium
(*E-mail: fedro.peccatori@ieo.it)

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disclosure

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