Short communication

Long-term patient reported outcomes and hematologic toxicity among patients who received Granulocyte-Colony Stimulating Factors during chemotherapy for early breast cancer

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ABSTRACT

We assessed long-term associations of Granulocyte-Colony Stimulating Factors (G-CSF) use with patient-reported outcomes (PROs) and hematologic toxicity among chemotherapy-treated, early-stage breast cancer patients in CANTO (NCT01993498).

Among 2920 patients longitudinally followed-up until year-4 after diagnosis, 49% used G-CSF. In multivariable-adjusted mixed-models, EORTC QLQ-C30 pain and summary score were not substantially different between groups (overall adjusted mean difference, use vs no-use [95%CI]: +1.27 [-0.33 to +2.87] and −1.01 [-1.98 to −0.04], respectively). PROs were slightly worse at year-4 among patients receiving G-CSF, although differences were of trivial clinical significance. No major differences were observed in leukocyte or platelet count over time.

1. Introduction

Adjuvant chemotherapy reduces recurrence risk and improves survival in women with early breast cancer (EBC). Patients with unfavorable prognostic clinical, pathological, and molecular features, including stage II or III BC, Human Epidermal Growth Factor Receptor 2 (HER2) overexpressing BC, triple-negative BC or estrogen-receptor positive BC with unfavorable genomic signatures, typically derive bigger absolute benefit from such strategy [1,2]. Nevertheless, chemotherapy can induce relevant hematologic toxicities, namely leukopenia, neutropenia and febrile neutropenia (FN), which are important limiting factors in cycles spacing, potentially leading to serious morbidity and complications [3—5]. Granulocyte colony-stimulating factors (G-CSF) are able to reduce

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the incidence of FN, with the relative risk of FN being almost halved among patients receiving G-CSF during standard chemotherapy [6–9]. This allows pre-defined chemotherapy schedules and avoiding delays, particularly in dose-dense regimens [10,11]. G-CSF are generally well tolerated, although some short-term toxicities were reported, most frequently medullary bone pain (25–36%) [12,13]. Other adverse reactions include leukocytosis, transient thrombocytopenia and transient reversible alterations in chemistries [12–21]. Very few data exist about long-term toxicities and impact on patient-reported quality of life (QOL) [22]. We aimed to assess associations between G-CSF utilization and long-term variation in patient reported outcomes (PROs) and hematologic values, using CANTO data (CANcer TOxicities cohort; NCT01993498). CANTO is a prospective, multicenter study that enrolled patients with stage I-II-III BC across 26 centers in France. The study collects extensive longitudinal clinical, sociodemographic, tumor, treatment, and PROs data, with the specific purpose of characterizing long-term toxicities of BC and its treatments. Patients are assessed at diagnosis and at several time-points during follow-up after primary treatment completion, which includes surgery, chemo- and/or radiation-therapy, whatever comes last. Endocrine and anti-HER2 treatment could be ongoing in the follow-up phases. All participants provided informed consent and the study was approved by the national regulatory and ethics committee (ID-RCB:2011-A01095-36,11−039). Study procedures were previously described [23].

2. Methods

We used data of 6619 women with EBC from CANTO, with available follow-up until year-4 post-diagnosis (Fig. 1). Per protocol, CANTO patients are censored at BC recurrence. Our primary outcome was pain, assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QOL questionnaire (QLQ)-C30 v3.0 [24]. Exploratory outcomes were QLQ C30-Summary Score [25–27], all other QLQ-C30 domains, leukocyte and platelet counts. PROs were longitudinally collected at diagnosis (baseline), year-1, year-2- and year-4 post-diagnosis. Hematological values were obtained from blood samples at diagnosis, at year-1 and year-4 post-diagnosis. G-CSF use (yes vs no) was our independent variable.

We used longitudinal mixed models to assess associations between G-CSF use and continuous outcomes. Covariates included time, G-CSF use-by-time interaction and cohort characteristics (categorized per Table 1). We obtained model-based, multivariable-adjusted mean values within groups, mean between-group differences (G-CSF use vs no) and respective 95% Confidence Intervals (CI) at each time point for each outcome. Adjustment factors were chosen based on differences in univariate tests between groups (p < 0.05) and variables of *a priori* clinical interest.
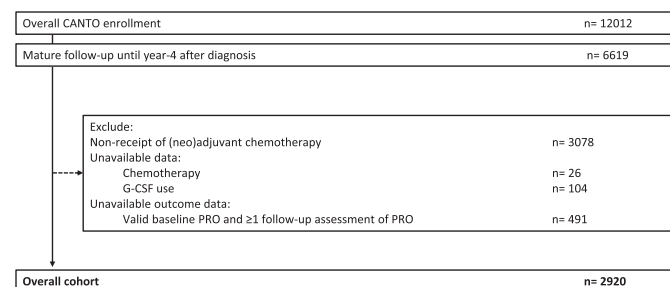

Overall CANTO enrollment	n= 12012
Mature follow-up until year-4 after diagnosis	n= 6619
Exclude: Non-receipt of (neo)adjuvant chemotherapy	n= 3078
Unavailable data: Chemotherapy	n= 26
G-CSF use	n= 104
Unavailable outcome data: Valid baseline PRO and ≥1 follow-up assessment of PRO	n= 491
Overall cohort	**n= 2920**

Fig. 1. CONSORT diagram of patient population. G-CSF = Granulocyte-Colony Stimulating Factors; PRO = patient-reported outcomes.

Statistical analysis was performed using R studio (R version 3.6.2) and SAS statistical software Version 9.4 (SAS Institute Inc.). Statistical significance was defined with a 2-sided p-value<0.05.

3. Results

Cohort description. We included 2920 women treated with chemotherapy that had available information on G-CSF use and primary outcome assessments (Fig. 1). Mean age was 52.7 years (Standard Deviation [SD] 11.0). Most women (86.3%) received anthracycline-taxane containing regimens (FAC/FEC + docetaxel = 85.1%). 1422 patients (48.7%) received G-CSF (long-acting [pegfilgrastim] = 47.5%, short-acting [filgrastim or lenograstim] = 28.3%, combinations of the two = 9.4%, others = 13%). Mean duration of G-CSF treatment was 12.3 weeks (SD 13.8). Patients receiving G-CSF were older, more frequently had higher stage BC, underwent axillary dissection and received aromatase inhibitor (AI) vs. those not receiving G-CSF (Table 1).

PROs and hematological values by G-CSF use. Patients receiving G-CSF seemed to have worse baseline PROs, including lower Summary Score (Fig. 2 and Table 2).

Over time, pain score was not statistically different between groups, with an adjusted overall mean difference (adjMD) (vs no G-CSF use) of +1.27 (95% CI -0.33 to +2.87). The trajectory of C30-Summary Score behaved similarly, with an adjMD (vs no G-CSF use) of −1.01 (95% CI -1.98 to −0.04). Fig. 2 displays mean values by group (**2A,B**) and mean differences vs no G-CSF in pain and C30 Summary Score at each time point (**2C,D**). For both outcomes, we observed slightly worse scores at year-4 post-diagnosis among patients receiving G-CSF (Fig. 2C and D). Consistently, other evaluated PROs were substantially similar between groups (Table 2, Supplementary Table 1**).**

No major differences were observed in leukocyte or platelet count (overall adjMD vs no-G-CSF use [95% CI]: −281 cells/mm^3 [-394 to −168] and −255 cells/mm^3 [-4452 to +3942], respectively [Fig. 2E,G and 2F,H, respectively]) (Table 2 and Supplementary Table 1 show between-group differences and mean scores by group at each time point).

4. Discussion

In this CANTO sub-study, we observed similar patterns in QOL and hematological values between patients receiving G-CSF or not during (neo)adjuvant chemotherapy for EBC. All explored outcomes followed almost superimposable long-term trajectories.

Among patients receiving G-CSF, several short-term side effects were previously described and some biological mechanisms were proposed. G-CSF are thought to trigger medullary bone pain through bone marrow expansion, activation of pro-inflammatory circuits and sensitization of peripheral nerve fibers to pain stimuli [28–30]. In addition, after a prolonged G-CSF-stimulated granulopoiesis, the number of erythropoietic progenitors may decline, favoring the onset of anemia and thrombocytopenia [12,17,18,21]. Building on this, we hypothesized that some inflammatory and hematopoietic alterations may persist in patients receiving G-CSF, resulting in worse pain, worse PROs and hematologic toxicity over time. Although minor differences were present at later time-points in our analysis, suggesting a slightly worse status among patients treated with G-CSF (e.g., pain score +2.75 points at year-4), differences of such small magnitude may have only trivial clinical significance, as reported by Cocks K [31]. In addition, the overall trend of similar trajectories between groups does not indicate substantial detrimental effects of G-CSF on long-term QOL and hematological profile. Strengths of our study include its large sample, longitudinal design and availability of socio-demographic,

Table 1
Cohort characteristics overall and by use of G-CSF.

N (%)	Whole cohort	By use of G-CSF		
		Yes	No	p*
Total	2920 (%)	1422 (48.7%)	1498 (51.3%)	
Age at diagnosis, years				
Mean (SD)	52.7 (11.0)	53.4 (11.3)	52.1 (10.7)	<0.001
Missing	—	—	—	
Marital Status				
In a relationship	2086 (74.6)	1044 (76.0)	1042 (73.2)	0.097
Not in a relationship	712 (25.4)	330 (24.0)	382 (26.8)	
Missing	122	48	74	
Highest education level				
Primary or lower	370 (13.1)	191 (13.8)	179 (12.4)	0.122
High school	1298 (45.9)	651 (47.1)	647 (44.8)	
College graduate or higher	1159 (41.0)	541 (39.1)	618 (42.8)	
Missing	93	39	54	
Menopausal status				
Premenopausal	1380 (48.1)	619 (44.6)	761 (51.5)	<0.001
Postmenopausal	1487 (51.9)	770 (55.4)	717 (48.5)	
Missing	53	33	20	
Charlson Comorbidity Index				
0	2179 (81.0)	1033 (80.4)	1146 (81.6)	0.443
1+	510 (19.0)	252 (19.6)	258 (18.4)	
Missing	231	137	94	
Smoking behavior				
Active smoker	537 (18.6)	233 (16.6)	304 (20.6)	0.006
Former/Never smoker	2344 (81.4)	1173 (83.4)	1172 (79.4)	
Missing	39	16	23	
Tumor stage				
I	792 (27.2)	373 (26.3)	419 (28.0)	0.032
II	1607 (55.1)	768 (54.1)	839 (56.0)	
III	518 (17.7)	279 (19.6)	239 (16.0)	
Missing	3	2	1	
Breast surgery				
Partial surgery	1834 (62.8)	874 (61.5)	960 (64.1)	0.154
Mastectomy	1086 (37.2)	548 (38.5)	538 (35.9)	
Missing	—	—	—	
Axillary surgery				
Sentinel lymph node	1181 (40.4)	548 (38.5)	633 (42.3)	0.045
Axillary dissection	1739 (59.6)	874 (61.5)	865 (57.7)	
Missing	—	—	—	
Chemotherapy				
Adjuvant	2272 (77.8)	1115 (78.4)	1157 (77.2)	0.472
Neoadjuvant	648 (22.2)	307 (21.6)	341 (22.8)	
Missing	—	—	—	
Type of chemotherapy				
Anthracyclines	118 (4.0)	63 (4.4)	55 (3.7)	0.340
Taxanes	283 (9.7)	129 (9.1)	154 (10.3)	
Anthracyclines and Taxanes	2519 (86.3)	1230 (86.5)	1289 (86.0)	
Missing	—	—	—	
Adjuvant radiation therapy				
No	194 (6.7)	91 (6.4)	103 (6.9)	0.662
Yes	2723 (93.3)	1329 (93.6)	1394 (93.1)	
Missing	3	2	1	
Endocrine therapy				
Tamoxifen	856 (29.4)	394 (27.8)	462 (30.9)	0.019
Aromatase Inhibitor	1348 (46.3)	694 (49.0)	654 (43.8)	
No	707 (24.3)	329 (23.2)	378 (25.3)	
Missing	9	5	4	
Anti-HER2 therapy				
No	2279 (78.1)	1134 (79.8)	1145 (76.4)	0.031
Yes	640 (21.9)	287 (20.2)	353 (23.6)	
Missing	1	1	—	

*The distribution of variables by G-CSF use was described with Wilcoxon test for continuous variables and with chi-square tests for categorical variables.
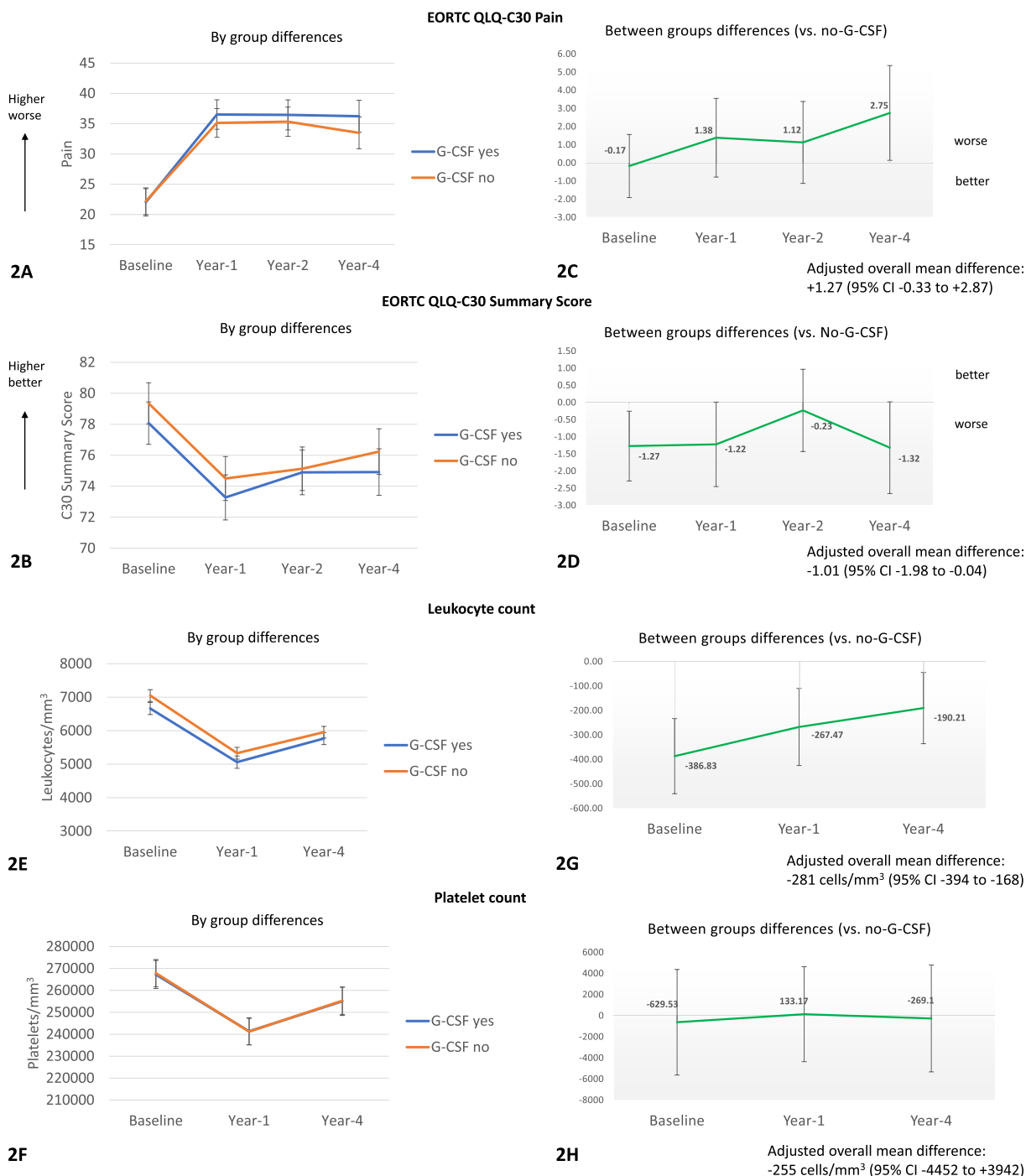G-CSF = Granulocyte Colony-Stimulating Factors; SD= Standard Deviation; HER= Human Epidermal growth factor Receptor.

Fig. 2. Mean model-based pain and Summary Score values (EORTC QLQ-C30) over time (2A, B) and between-group differences (2C, D) in pain and Summary Score (G-CSF use vs no). Mean model-based leukocyte and platelet count values over time (2E, F) and between-group differences (2G, H) in leukocyte and platelet count (G-CSF use vs no). C30 Summary Score is calculated using the mean scores for 13 of the 15 QLQ-C30 domains (the Global Health and the Financial Impact scales are not included) and has appeared to have stronger prognostic value for overall survival than single QLQ-C30 domains. For functional scales, higher scores and a positive difference indicate a better condition. Vice versa, for symptom scales higher scores and a positive difference are indicative of a worse symptomatology. 95% Confidence Interval around the mean difference not crossing 0 indicates a statistically significant difference.

clinical and treatment data, allowing to adjust our analyses. Nevertheless, we acknowledge some residual selection bias, as there were baseline and treatment differences between the groups and potential unmeasurable confounders beyond adjustment factors. For example, patients receiving G-CSF scored slightly worse at diagnosis, denoting a poorer initial clinical condition, and received more frequently adjuvant treatments that may lead to increased

patient-reported pain (e.g., AI). Statistical adjustment may not be able to fully address such differences.

In conclusion, G-CSF seemed overall well-tolerated in our cohort, with no major clinical impact on PROs and hematologic toxicity on the long run. Although we did not report safety concerns or specific warning signals about long-term impact of G-CSF use in this study, appropriate G-CSF administration during chemotherapy

Table 2
Mean between-group differences (G-CSF use vs no) in patient-reported outcomes and hematological values.

Outcome	Diagnosis (baseline)		Year-1		Year-2		Year-4	
	Mean difference vs no G-CSF	95% CI	Mean difference vs no G-CSF	95% CI	Mean difference vs no G-CSF	95% CI	Mean difference vs no G-CSF	95% CI
EORTC QLQ-C30 Functional Scales								
Global Health	−1.72	**−3.24 to −0.21**	−1.35	−2.83 to +0.14	−0.29	−1.81 to +1.23	−0.73	−2.54 to +1.08
Physical Function	−0.58	−1.62 to +0.45	−0.78	−2.03 to +0.46	−0.43	−1.72 to +0.86	−0.95	−2.38 to +0.48
Emotional Function	−0.68	−2.60 to +1.24	−0.37	−2.34 to +1.60	+0.76	−1.28 to +2.80	−0.28	−2.64 to +2.08
Social Function	−0.67	−2.20 to +0.85	−1.30	−3.35 to +0.75	+1.29	−0.60 to +3.18	−0.67	−2.86 to +1.53
Cognitive Function	−1.31	−3.03 to +0.40	+0.12	−1.87 to +2.11	+0.41	−1.65 to +2.47	−1.29	−3.60 to +1.02
Role Function	−1.99	**−3.78 to −0.20**	−1.87	−3.91 to +0.17	−0.60	−2.59 to +1.40	−2.24	−4.47 to +0.002
EORTC QLQ-C30 Symptom Scales								
Fatigue	+1.14	−0.76 to +3.03	+1.56	−0.49 to +3.61	+0.44	−1.60 to +2.48	+0.41	−1.94 to +2.76
Insomnia	+2.08	−0.58 to +4.74	+2.20	−0.61 to +4.99	−0.20	−3.08 to +2.68	−0.47	−3.79 to +2.84
Nausea/Vomit	+0.08	−0.86 to +1.01	+0.30	−0.84 to +1.44	−0.91	−1.99 to +0.17	−0.13	−1.46 to +1.21
Dyspnea	+1.38	−0.29 to +3.05	+1.07	−1.07 to +3.20	+1.23	−0.91 to +3.38	+2.78	**+0.31 to +5.26**
Appetite Loss	+1.18	−0.84 to +3.19	+0.46	−1.24 to +2.16	−1.16	−2.71 to +0.40	+1.57	−0.41 to +3.55
Constipation	+1.75	**+0.02 to +3.48**	+2.74	**+0.63 to +4.86**	+3.98	**+1.68 to +6.27**	+1.93	−0.67 to +4.53
Diarrhea	+0.27	−1.20 to +1.74	−0.11	−1.83 to +1.61	−2.00	**−3.63 to −0.37**	+0.76	−1.33 to +2.84
Financial difficulties	−0.04	−1.59 to +1.50	+0.13	−2.04 to +2.31	+0.22	−1.67 to +2.11	+1.50	−0.38 to +3.39
Hematological values								
Leukocyte count (count/mm³)	−387	**−540 to −233**	−267	**−425 to −110**	N.A.	N.A.	−190	**−336 to −45**
Platelet count (count/mm³)	−629	−5630 to +4371	+133	−4364 to +4630	N.A.	N.A.	−269	−5333 to +4794

Estimates were obtained from a mixed model including G-CSF use, time, G-CSF use*time interaction, and covariates: age, marital status, education level, Charlson score, smoke behavior, stage of disease, breast surgery, axillary surgery, type of chemo- and endocrine therapy, anti-HER2 therapy (categorized as in Table 1). All reported values are model-based, multivariable-adjusted average scores. For functional scales, a positive difference indicates a better condition. Vice versa, for symptom scales a positive difference is indicative of a worse symptomatology. 95% Confidence Interval around the mean difference not crossing 0 is bolded and indicates a statistically significant difference.
G-CSF = Granulocyte Colony-Stimulating Factors; CI= Confidence Interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; N.A. = not assessed.

for EBC is warranted. A number of reports documented G-CSF overuse in clinical practice, with 10%—62% of patients receiving G-CSF as prophylaxis during regimens at low-risk for neutropenic events or as therapy for existing FN [32—35]. G-CSF support should be provided as recommended by dedicated guidelines [6] and in the setting of emerging algorithms, suggesting feasibility and safety of its omission while respecting pre-specified safety rules [36].

Ethical approval

The CANTO study was approved by the national regulatory authorities of France (ID-RCB: 2011-A01095-36) and by the ethics committee CPP IDF VII (11—039). Informed consent for study participation was obtained at patient enrollment.

Data availability

CANTO data is available upon request to a dedicated study Executive Committee (http://www.unicancer.fr/rd-unicancer/letude-canto).

Previous presentations

This manuscript contains original material. Portions of this work were presented in the Mini Oral session of the ESMO Virtual Congress on September 18, 2020 (https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/long-term-patient-reported-outcomes-pro-and-hematologic-toxicity-among-patients-pts-who-received-granulocyte-colony-stimulating-factors-g-csf; Annals of Oncology (2020) 31 (suppl_4): S988—S1017. 10.1016/annonc/annonc291). This study was also recognized with an ESMO Merit Award to Dr. Lapidari.

Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.02.014.

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