

# Impact of Chemotherapy-induced Menopause in Women of Childbearing Age With Non-metastatic Breast Cancer – Preliminary Results From the MENOCOR Study

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## Abstract

**In our study, we evaluated the quality of life of young women experiencing chemotherapy-induced menopause. Our results underline that age and pre-treatment anti-Müllerian hormone level could be helpful to predict the menopause but these results have to be confirmed in further studies. At 6 months post-chemotherapy, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast 23 (QLQ-BR23) questionnaire tended to highlight an impaired quality of life in menopausal patients.**

**Background:** Young patients with breast cancer treated with chemotherapy can experience ovarian failure, which can lead to chemotherapy-induced menopause (CIM) impacting the quality of life (QoL). A prospective study was set out to evaluate the impact of CIM on QoL in women of childbearing age with non-metastatic breast cancer, and this article reports results of the interim analysis conducted to evaluate feasibility and to see preliminary results. **Patients and Methods:** A total of 58 women (age, 18-46 years) with newly diagnosed breast cancer and treated with chemotherapy were eligible. QoL was assessed by self-administered questionnaires (Quality of Life Questionnaire-Core 30 [QLQ-C30], Quality of Life Questionnaire-Breast 23 [QLQ-BR23], and Kupperman index) and hormonal variations (anti-Müllerian hormone [AMH], follicle-stimulating hormone, and estradiol) were explored. We compared patients with  $\geq 12$  months amenorrhea (CIM) ( $n = 41$ ) to patients with  $< 12$  months of amenorrhea (non-CIM) ( $n = 17$ ). **Results:** A good inclusion rate (approximately 4/month) and sufficient data enabled us to perform this analysis. QLQ-C30 failed to show any difference between CIM and non-CIM patients ( $P = .5$ ). In contrast, at 6 months post-chemotherapy, CIM patients tended to have lower QoL as shown by QLQ-BR23 ( $P = .16$ ) and more severe climacteric symptoms ( $P = .01$ ). Regarding hormonal variations, AMH pre-treatment level was higher in non-CIM patients ( $P = .0032$ ). We also noted that CIM patients were older ( $P = .00013$ ), had shorter menstruation cycle ( $P = .082$ ), and experienced faster amenorrhea ( $P = .088$ ). **Conclusions:** The study is technically feasible, and our preliminary results underline that age in association with pre-treatment AMH level could be helpful to predict ovarian function. QLQ-BR23 seemed to be stronger, more precise, and appropriate to evaluate QoL changes in patients with breast cancer than the QLQ-C30.

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**Keywords:** Gonadotoxicity, Hormonal variations, Ovarian reserve, Quality of life, Young women

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## Introduction

Breast cancer is the most common cancer among women, and about 12% to 20% of patients are of childbearing age.<sup>1-3</sup> Young women with breast cancer are known to have the poorest prognosis owing to the aggressiveness of the tumor, and they are mostly treated with chemotherapy.<sup>4,5</sup> Despite the fact that chemotherapy improves survival and reduces the risk of recurrence,<sup>6,7</sup> it could cause ovarian failure, leading to chemotherapy-induced amenorrhea (CIA) or premature menopause.<sup>1,8</sup> Some studies reported the complexities in defining the natural menopause, but it is even more difficult in the case of young women treated with chemotherapy.<sup>9,10</sup>

According to the World Health Organization (WHO), menopause is characterized by at least 1 year of amenorrhea.<sup>11</sup> Other definitions found in the literature vary considerably and describe menopause as a minimum of 1 to 2 years of amenorrhea.<sup>12,13</sup> Hormonal changes are also considered for its definition. Among post-menopausal women, anti-Müllerian hormone (AMH) and estradiol serum levels decrease, whereas follicle-stimulating hormone (FSH) serum level increases.<sup>14</sup> Currently, AMH is considered to be a good marker of ovarian reserve<sup>15</sup> and could play a role in the prediction of chemotherapy-induced menopause (CIM) in young patients with cancer.<sup>16</sup>

Today, patient quality of life (QoL) is a central concern and an integral part of medical care.<sup>17-19</sup> Some studies have documented impaired QoL in survivors of breast cancer. In particular, young patients with breast cancer are at greater risk of impaired health-related QoL, including psychological disturbance, sexual problems, or physical changes, but very few studies have examined the specific case of women experiencing CIM.<sup>18,20-23</sup> Moreover, the clear identification of menopause in patients treated by chemotherapy could be helpful to determine the appropriate endocrine therapy (eg, tamoxifen or aromatase inhibitors) when hormone receptors are expressed.<sup>18,20,23</sup>

In order to clarify these issues, we conducted a prospective study (MENOCOR [Impact of Chemotherapy-induced Menopause on the Quality of Life in Young Women of Childbearing Age and Diagnosed With Non-metastatic Breast Cancer]) on young women diagnosed with non-metastatic breast cancer. The primary endpoint is to assess the impact of CIM on the functional dimension of QoL using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) functional score. The secondary endpoints are hormonal variations (AMH, estradiol, and FSH) and specific aspects of QoL based on menopausal status. An interim analysis of this study was performed to determine the feasibility of the study and see the preliminary results.

## Patients and Methods

### Patients

Eligible patients were women aged 18 to 45 years, with stage I to III breast cancer, without amenorrhea and scheduled for treatment with adjuvant or neoadjuvant chemotherapy. Age over 45 years, metastatic cancer, previous chemotherapy or hormonotherapy, hysterectomy or oophorectomy, and menopause were exclusion criteria. A total of 240 patients are expected to participate in this study, and an interim analysis was scheduled after the inclusion of at least 60 patients with outcomes at 1.5 years follow-up (ie, 12 months post-chemotherapy).

### Study Design

This is a prospective, multicenter study, approved by the CPP Sud Est VI Ethics Committee (08/11/2013) and registered at ClinicalTrials.gov (NCT02102568). A total of 63 patients were enrolled from April 2014 to June 2015 in the 3 participating centers: Jean Perrin Cancer Center (Clermont-Ferrand), Lucien Neuwirth Cancer Institute (Saint-Etienne), and Jean Godinot Cancer Institute (Reims). All patients provided informed consent.

After enrollment, patients were asked about their medical and gynecologic history. Breast cancer characteristics and physical activity were also recorded. Before chemotherapy, a complete biology report was drawn up for each patient according to the study provisions to ascertain the eligibility of the patient. The duration of patient participation in the trial is about 3 years, with an average of 6 months chemotherapy and a follow-up of 2.5 years (Figure 1).

### Study Endpoints

This interim analysis has been planned in order to evaluate the feasibility of the study: rhythm of inclusion, patients' responses, and data collection. Preliminary results concerning the incidence of women with 12 months of amenorrhea, the primary endpoint, the Quality of Life Questionnaire-Breast 23 (QLQ-BR23) scores, vasomotor symptoms, and their hormonal variations were evaluated for this interim analysis. It was conducted after the enrolment of 63 patients in the study, 1.5 years after inclusion (ie, 12 months after chemotherapy). These results will be compared with data available at the end of the study, and we will see if the 12 months of amenorrhea is predictive of menopause or not.

Because this study does not expose patients to a supplementary risk, this interim analysis will not request an interruption of inclusions.

### Menopausal Status

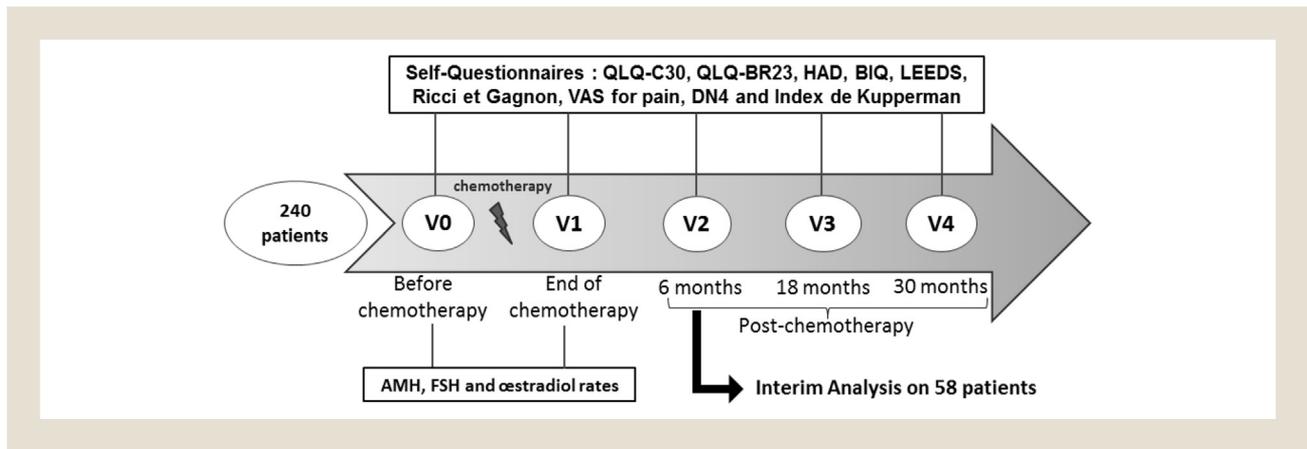
To identify the menopausal status of each patient at the end of the study and classify them into 2 groups — chemotherapy-induced menopause (CIM) and absence of chemotherapy-induced menopause (non-CIM) — information about their menstruation cycle was collected throughout the study, and menopause was defined as  $\geq 2$  years of amenorrhea. For this purpose, each patient was asked about the dates of her last menstruation before enrollment, before every chemotherapy cycle, and at each follow-up, the time to onset of amenorrhea if present, the return of menstruation if applicable, and the duration of amenorrhea. A calendar where patients noted their menstruation dates was issued at inclusion.

In order to perform the interim analysis conducted on data available at 1.5 years of follow-up, 2 groups of patients were defined according to their amenorrhea duration, and menopause is characterized by at least 1 year of amenorrhea as defined by the WHO<sup>11</sup>: CIM with  $\geq 12$  months of amenorrhea and non-CIM with  $< 12$  months of amenorrhea.

### Self-administered Questionnaires

To assess QoL, patients were asked to complete the questionnaires several times during their participation in the study: at inclusion before chemotherapy (V0), at the end of chemotherapy (V1), 6 months (V2), 18 months (V3), and 30 months (V4) post-chemotherapy (Figure 1). In accordance with the study, this interim

**Figure 1** Study Design. A Total of 240 Patients are Expected to Participate in This Study, and the Interim Analysis Was Conducted on 58 Patients. To Assess Quality of Life, Patients Were Asked to Complete the Questionnaires Several Times: At Inclusion Before Chemotherapy (V0), at the End of Chemotherapy (V1), 6 Months Post-Chemotherapy (V2), 18 Months Post-Chemotherapy (V3), and 30 Months Post-Chemotherapy (V4). Hormonal Measurements (AMH, FSH, and Estradiol) Were Done before Chemotherapy (V0) and at the End of Chemotherapy (V1)



Abbreviations: AMH = anti-Müllerian hormone; BIQ = Body Image Questionnaire; DN4 = neuropathic pain in 4 questions; FSH = follicle-stimulating hormone; HAD = Hospital Anxiety Depression scale; LEEDS = sleeping quality questionnaire; QLQ-BR23 = Quality of Life Questionnaire-Breast 23; QLQ-C30 = Quality of Life Questionnaire-Core 30; VAS = Visual Analogue Scale.

analysis focused on data available at inclusion, at the end of the treatment (approximately 6 months follow-up), and at 6 months post-chemotherapy (ie, 1 year follow-up).

The primary outcome (ie, the impact of CIM on functional QoL), was assessed using the QLQ-C30 functional score.<sup>24</sup> The EORTC QLQ-C30 evaluates general QoL in oncology, it is divided into 3 scores: symptom, functional, and global, and comprises a total of 30 items. The functional part of this questionnaire comprises 15 items divided into 5 dimensions: physical activity, daily activity, emotional status, cognition, and social life. The total functional score is a percentage calculated by the average of all dimensions. In the STIC RMI [support of innovative and expensive techniques – immediate breast reconstruction] study,<sup>25</sup> menopausal women scored 5 points lower for the QLQ-C30 functional score compared with non-menopausal women, so the same difference was expected between our CIM and non-CIM patients after 2 years of amenorrhea. For this interim analysis, conducted only 6 months after chemotherapy, the differential of variation between the CIM and non-CIM groups is evaluated. A high score indicates good QoL.<sup>24</sup>

The EORTC QLQ-BR23 is used in combination with the EORTC QLQ-C30 and addresses specific issues of breast cancer. Like the QLQ-C30, it contains 2 dimensions, one for symptoms and the other one for functions, with a total of 23 items scored from 1 to 4. It particularly investigates body image, sexuality, and pain. The total score is a percentage calculated by the average of all dimensions. In our study, a high score indicates good QoL.<sup>26</sup>

The Kupperman index is a specific questionnaire on climacteric symptoms. It contains 11 items with scores ranging from 0 to 3. The global score is calculated by attributing a specific weight to each item, and can vary from 0 to 51. A higher score indicates more severe climacteric symptoms.<sup>27</sup>

Because of the large number of questionnaires used in this study, this interim analysis focused on the most relevant results.

## Hormones

To study hormone variations (AMH, estradiol, and FSH) for menopause prediction, measurements were conducted 2 times: before chemotherapy and 1 month after chemotherapy. Because no other hormonal dosages are expected for these patients, it allowed us to see the preliminary result for this interim analysis.

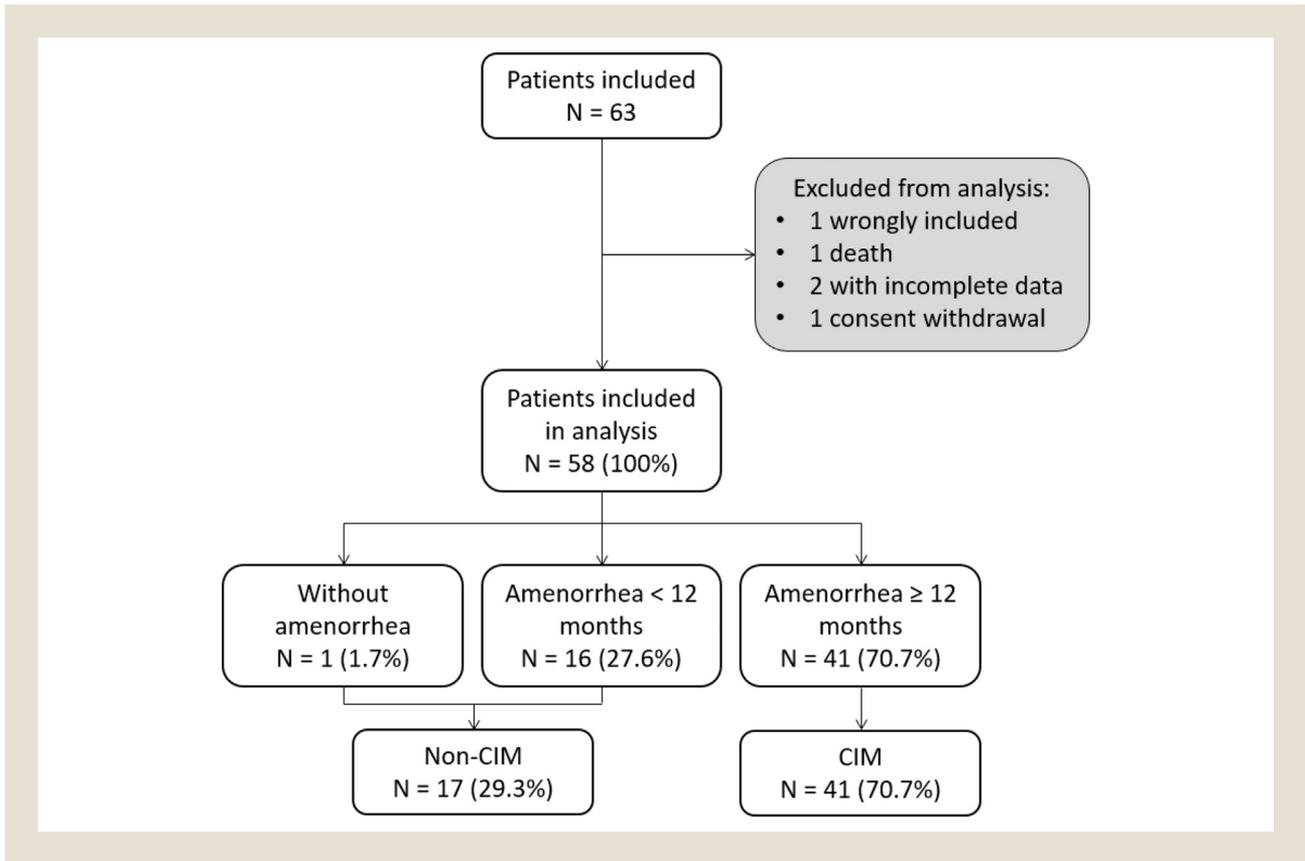
Concerning AMH, blood samples were collected, and serum levels were measured by an external laboratory using electrochemiluminescence immunoassays on Roche Cobas 8000. According to the laboratory, AMH ranges between 0.7 and 52 pmol/L in women aged from 20 to 44 years; between 0.3 and 14.7 pmol/L in women aged from 45 to 50 years, and is undetectable in menopausal women. The detection threshold was 0.21 pmol/L with a variation coefficient < 1.8%.

Estradiol and FSH were measured in the hospital laboratory or in an ordinary analytical laboratory by chemiluminescence immunoassay. Estradiol and FSH in non-menopausal women ranges between 79 and 1348 pmol/L and 1.7 to 17.5, respectively. In menopausal women, estradiol is < 214 pmol/L, and FSH is between 12.7 and 132.2 UI/L. The detection thresholds were 40 pmol/L and 0.2 UI/L, respectively, for estradiol and FSH.

## Statistical Analysis

Patient characteristics were described using standard distribution parameters: means  $\pm$  standard deviation and range for quantitative parameters (and median for non-Gaussian distributions), and counts and frequencies (%) for categorical parameters. To study the evolution of questionnaire scores over time, a 2-way analysis of variance model (mixed model) was used. Statistical relationships between pairs of variables were explored using  $\chi^2$  tests for categorical parameters, *t* tests, or analysis of variance when one parameter was quantitative (or the Mann-Whitney *U* test or Kruskal-Wallis *H* test in case of non-Gaussian distribution and/or heteroscedasticity), and with 2 quantitative parameters, the Pearson

Figure 2 Flowchart of Participants



Abbreviation: CIM = chemotherapy-induced menopause.

correlation coefficient (or for non-Gaussian distributions, the Spearman rank correlation). To compare the evolution of quantitative parameters before and after chemotherapy, the Student paired  $t$  test was used. A multivariate analysis of factors influencing CIM was performed using a logistic regression model. All tests were 2-sided. Significance was set at the standard  $P$ -value of  $P \leq .05$ . Data management and statistical calculations were performed on SEM software.<sup>28</sup>

## Results

### Patient Characteristics

A total of 63 patients were enrolled from April 2014 to June 2015. Among them, 5 were excluded from the interim analysis: 1 patient was wrongly included, another died during the study, for 2 patients there was too much missing data to perform the analysis, and 1 patient withdrew her consent (Figure 2). A total of 58 patients were included in this interim analysis, and their characteristics are shown in Table 1. The median age at enrollment was 40.8 years (range, 24.7-46 years). Ninety-eight percent of patients presented a grade II/III tumor, and 21% were human epidermal growth factor receptor 2-positive.

### Feasibility and Recruitment

A total of 63 patients were enrolled in 15 months, which means an average of 4 patients were newly included each month. The study

expects a total of 240 patients, which could be reached in approximately 5 years with the same inclusion rate. Of the 58 patients, 78% responded to questionnaires (Table 2), and 86% had hormone measurements (Table 3). This amount of data was sufficient to enable the calculation of our first estimates.

### Menopausal Status and Chemotherapy-induced Amenorrhea

Among the 58 patients, only 1 patient did not develop CIA and had regular menstrual cycles. Among the other 57 patients, 41 (70.7%) patients had at least 12 months of amenorrhea. Two groups of patients were defined on this basis: CIM  $\geq 12$  months of amenorrhea ( $n = 41$ ) and non-CIM < 12 months of amenorrhea ( $n = 17$ ) (Figure 2). Each group characteristics are shown in Table 1.

### Impact of CIM on QoL

The number of questionnaires per visit and per group is presented in Table 2.

### QLQ-C30 Functional Score

The QLQ-C30 functional score differed significantly in both patient groups between inclusion and 6 months post-chemotherapy ( $P = .013$ ). The score obtained at the end of chemotherapy was the lowest for both patient groups (CIM and non-CIM) and differed

# MENOCOR Study - An Interim Analysis

**Table 1 Patient Characteristics**

Characteristics	CIM and Non-CIM		CIM	Non-CIM	P Value
	N	%	N	N	
No. patients	58	100	41	17	—
Median age at enrollment, y (range)	40.8 (24.7-46) <sup>a</sup>	—	42.5 (33.3-46)	33.8 (24.7-44.1)	.00013 <sup>b</sup>
Body mass index, kg/m <sup>2</sup>					
Median (range)	22 (18-44)	—	22 (18-44)	22 (18-34)	.21
Underweight (<18.5)	4	7	2	2	1.00
Normal (18.5-24.9)	35	60	23	12	.67
Overweight (25-29.9)	9	16	8	1	.70
Obese (≥30)	10	17	8	2	1.00
Performance status					.79
0	51	88	37	14	—
1	4	7	2	2	—
2	1	2	1	0	—
Unknown	2	3	1	1	—
Children before chemotherapy					.48
No	7	12	4	3	—
≥1	51	88	37	14	—
Fertility preservation	7	12	2	5	.03 <sup>b</sup>
Smoking status					.19
Current	14	24	11	3	—
Former	16	28	13	3	—
Never	26	45	16	10	—
Breast cancer family history	30	52	20	10	.48
Histologic type					.30
Invasive ductal carcinoma	45	77.6	31	14	—
Invasive lobular carcinoma	5	8.6	5	0	—
Others	8	13.8	5	3	—
Histologic grade					.65
I	1	2	1	0	—
II/III	57	98	40	17	—
Nodal status					.27
Positive	27	47	21	6	—
Negative	31	53	20	11	—
Hormonal receptors					—
Estrogen-positive	43	74	30	13	.77
Progesterone-positive	32	55	23	9	.99
Human epidermal growth factor receptor 2-positive	12	21	8	4	.7
Neo-adjuvant chemotherapy	30	52	21	9	.9
Chemotherapy regimens					.29
3FEC + 3 Taxotere	31	52.5	22	9	—
4FEC + 4 Taxotere	11	18.6	9	2	—
6TAC	8	13.6	5	3	—
4AC + 4 T	6	10.2	5	1	—
4TAC	1	1.7	0	1	—
TCH	1	1.7	0	1	—

Abbreviations: AC = doxorubicin and cyclophosphamide; CIM = chemotherapy-induced menopause; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; T = docetaxel (or paclitaxel); TAC = docetaxel, adriamycin, and cyclophosphamide; TCH = docetaxel (or paclitaxel), carboplatin, and herceptin.

<sup>a</sup>One patient was 46 years old. She was included with the agreement of the study coordinator.

<sup>b</sup>Indicates a significant difference ( $P \leq .05$ ) between CIM and non-CIM patients.

**Table 2** Number of Questionnaires Per Group and Per Visit

No. Questionnaires	Inclusion (V0)		End of Chemotherapy (V1)		6 Months Post-chemotherapy (V2)	
	CIM	Non-CIM	CIM	Non-CIM	CIM	Non-CIM
QLQ-C30 functional score	38	17	34	14	30	14
QLQ-BR23 functional score	38	17	34	14	30	14
Kupperman Index	26	15	26	14	23	11

Abbreviations: CIM = chemotherapy-induced menopause; QLQ-C30 = Quality of Life Questionnaire-Core 30; QLQ-BR23 = Quality of Life Questionnaire-Breast 23.

significantly from inclusion ( $P = .0056$ ) and 6 months post-chemotherapy ( $P = .032$ ) (Figure 3A).

For the entire period (inclusion, end of chemotherapy, and 6 months post-chemotherapy), no difference was evidenced between CIM and non-CIM patients ( $P = .5$ ). The percentage of variation between inclusion and 6 months post-chemotherapy was a 2% decrease versus a 5% decrease for CIM and non-CIM patients, respectively, but this difference was not significant ( $P = .72$ ). Concerning the mean score at 6 months post-chemotherapy, the functional score differed only by 2 points between CIM and non-CIM patients (77.7 vs. 80.0;  $P = .76$ ) (Figure 3A).

### The QLQ-BR23 Functional Score: QoL Among Patients With Breast Cancer

As with the QLQ-C30 functional score, the QLQ-BR23 functional score varied significantly in both patient groups between inclusion and 6 months post-chemotherapy ( $P = .0025$ ). The score obtained at the end of chemotherapy was significantly lower from inclusion for the 2 groups of patients ( $P = .00073$ ). In contrast, difference between the end of chemotherapy and 6 months post-chemotherapy was not so clear ( $P = .12$ ) (Figure 3B).

Concerning the comparison of the 2 groups, no difference was evidenced between them for the entire period (inclusion, end of chemotherapy, and 6 months post-chemotherapy) ( $P = .33$ ). Between inclusion and 6 months post-chemotherapy, CIM patients had a 19% decrease, whereas non-CIM patients had a 3% decrease, and this difference was leaning towards significance ( $P = .16$ ). The comparison at 6 months post-chemotherapy reached near significance ( $P = .17$ ), with a lower mean score for CIM patients and a difference of 13 points (44.43 vs. 57.26) (Figure 3B).

### The Kupperman Index: Climateric Symptoms

Between inclusion and 6 months post-chemotherapy, the Kupperman Index showed a clear time effect ( $P < 10^{-7}$ ), with an increase of the score at the end of chemotherapy (Figure 3C).

The comparison between CIM and non-CIM patients was close to being significant ( $P = .084$ ). As expected, CIM patients had a significantly higher Kupperman Index at 6 months post-chemotherapy ( $P = .01$ ) (Figure 3C). The specific dimension analysis at 6 months post-chemotherapy showed nearly significant higher hot flushes and vaginal dryness in CIM patients than in non-CIM patients ( $P = .096$  and  $P = .091$ ). Mood depression was also significantly higher in CIM patients ( $P = .025$ ) (Figure 3D).

### Hormones

Hormone levels per group and per visit are presented in Table 3.

#### AMH Variations

In each group, pre-treatment level of AMH was significantly higher from post-treatment level ( $P < 10^{-7}$ ) (Figure 4A).

By comparing the 2 groups of patients, it was revealed that the variation of AMH level between inclusion and the end of chemotherapy was different, with a greater decrease in non-CIM patients ( $P = .0054$ ). Of course, the pre-treatment level was significantly higher in non-CIM patients ( $P = .0032$ ), but no difference was evident for the post-treatment level ( $P = .26$ ) (Figure 4A) (Table 3).

The analysis also showed a negative correlation between age and initial AMH; the older the patients were, the greater the decrease in AMH levels was ( $r^2 = 0.38$ ;  $P = 1.10^{-6}$ ) (Figure 4B).

#### FSH Variations

Between enrolment and after chemotherapy, the FSH level increased significantly in both groups of patients ( $P < 10^{-7}$ ) (data not shown).

No difference was observed between CIM and non-CIM patients for the variation of FSH level between these 2 periods ( $P = .25$ ). The difference between CIM and non-CIM patients was nearly significant for the pre-treatment level of FSH (10 UI/L vs. 5 UI/L;  $P = .07$ ) with a higher level in CIM patients, but this was not the case for the post-treatment level ( $P = .47$ ) (data not shown) (Table 3).

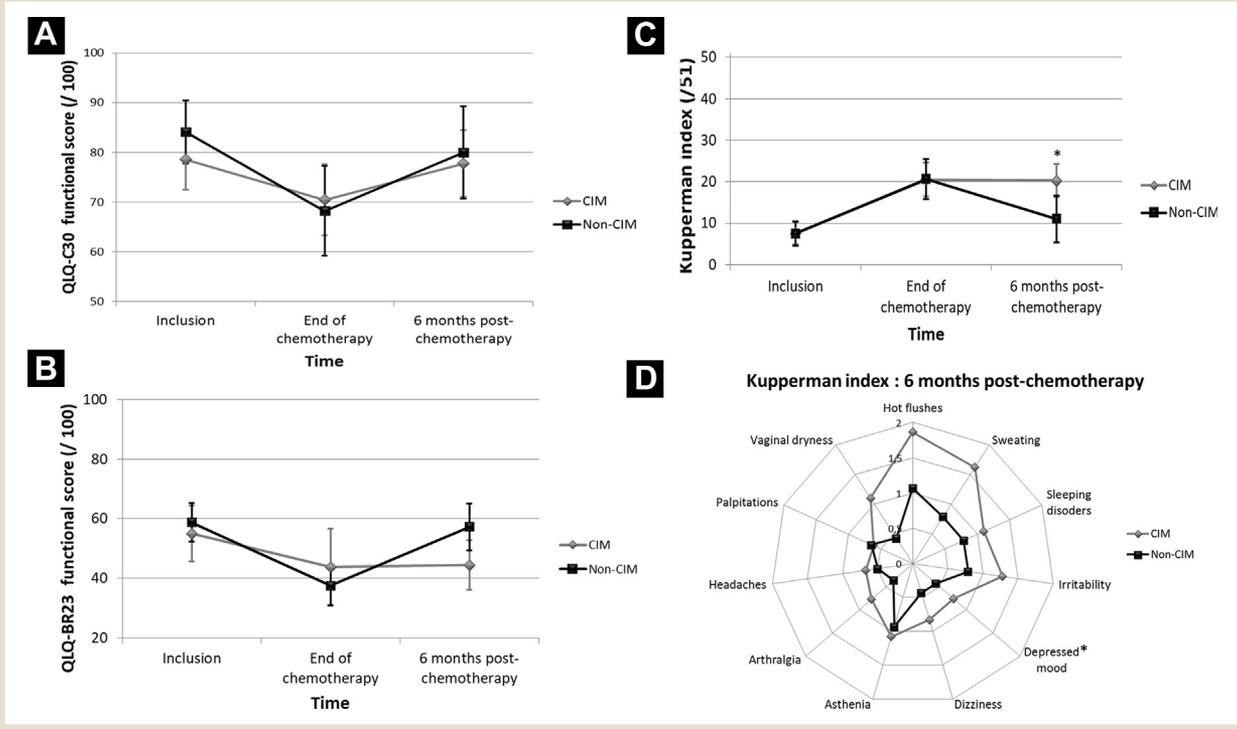
**Table 3** Hormone Levels Per Group and Per Visit

Hormones	Inclusion (V0)			End of Chemotherapy (V1)		
	CIM (Range)	Non-CIM (Range)	<i>P</i>	CIM (Range)	Non-CIM (Range)	<i>P</i>
AMH, pmol/L	3.93 (0.1-58.1) (N = 40)	13.5 (1.64-69) (N = 17)	.0032 <sup>a</sup>	0.1 (0-0) (N = 39)	0.1 (0.1-1.21) (N = 15)	.26
FSH, UI/L	5.7 (1.2-65) (N = 39)	4.5 (1.5-9.5) (N = 15)	.07	91.1 (16.7-198) (N = 28)	83 (11-117) (N = 12)	.47
Estradiol, pmol/L	327 (18.4-1527) (N = 39)	288 (131-782) (N = 15)	.49	40 (0-495) (N = 28)	24.5 (5-1073) (N = 12)	.94

Abbreviations: AMH = anti-Müllerian hormone; CIM = chemotherapy-induced menopause; FSH = follicle-stimulating hormone.

<sup>a</sup>Indicates a significant difference ( $P \leq .05$ ) between CIM and non-CIM patients.

**Figure 3** Quality of Life Measurements. A, QLQ-C30 Functional Score Variation From Inclusion to 6 Months Post-Chemotherapy: Mean ( $\pm 95\%$  Confidence Intervals). B, QLQ-BR23 Functional Score Variation From Inclusion to 6 Months Post-Chemotherapy: Mean ( $\pm 95\%$  Confidence Intervals). C, Kupperman Index Variation From Inclusion to 6 Months Post-Chemotherapy: Mean ( $\pm 95\%$  Confidence Intervals). D, Analysis per Dimension of Kupperman Index at 6 Months Post-chemotherapy. “\*\*” Indicates a Significant Difference ( $P \leq .05$ ) Between CIM and Non-CIM Patients



Abbreviations: CIM = chemotherapy-induced menopause; QLQ-BR23 = Quality of Life Questionnaire-Breast 23; QLQ-C30 = Quality of Life Questionnaire-Core 30.

**Estradiol Levels**

All patients saw their serum estradiol levels fall markedly between inclusion and the end of the treatment ( $P = .000014$ ) (data not shown).

No difference was evidenced between CIM and non-CIM patients for the estradiol level before chemotherapy ( $P = .49$ ), after chemotherapy ( $P = .94$ ), or for the variation between these 2 times ( $P = .36$ ) (data not shown) (Table 3).

**Risk Factors for CIM Patients (Univariate Analysis)**

The comparison of other characteristics between the CIM and non-CIM groups showed that CIM patients were 9 years older (43 vs. 34 years;  $P = .00013$ ), had done less fertility preservation ( $P = .03$ ), had a tendency to have shorter menstrual cycles ( $P = .082$ ), and had an earlier onset of amenorrhea during chemotherapy (no. of chemotherapy cycles before amenorrhea 3 vs. 4;  $P = .088$ ) (Table 1).

**Multivariate Analysis**

On multivariate analysis, only age was associated with menstrual status ( $P = .000022$ ); older patients have greater risk to experience premature menopause.

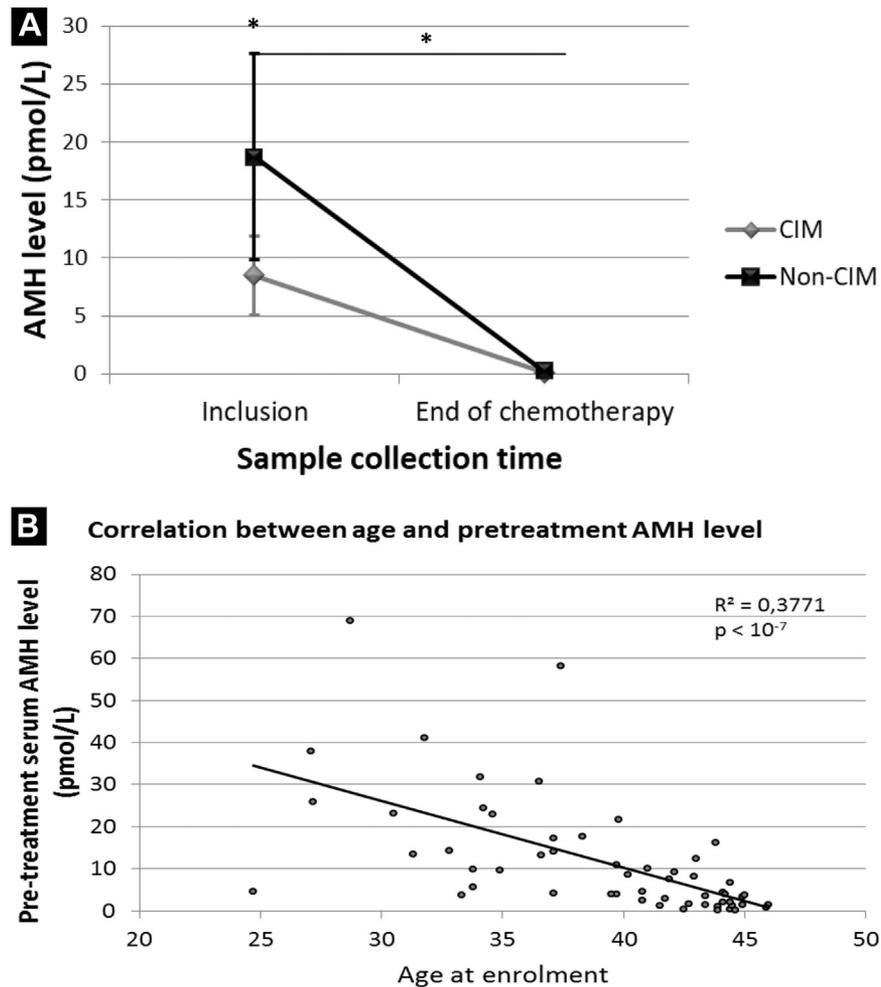
**Discussion**

In this prospective multicenter study, we conducted an interim analysis on data available at 1.5 years of follow-up (ie, 12 months post-chemotherapy), to see the feasibility and the preliminary results of the study.

A total of 63 patients have been enrolled in 15 months, showing a good inclusion rate and that the recruitment of the other 177 patients is technically feasible. Moreover the response rate ( $\approx 80\%$ ) of questionnaires and the hormone measurements were sufficient to perform this analysis and allow us to pursue this study. Particular attention should be given to questionnaires to limit the missing data in upcoming visits and patients.

To see the preliminary results of this study, we compared patients presenting at least 12 months of amenorrhea (CIM) to patients without amenorrhoea or with less than 12 months of amenorrhea (non-CIM). In this analysis, among our 58 patients, 98.3% of the patients experienced CIA, and 70.7% had long-term amenorrhea (or CIM) lasting at least 12 months. The incidence of CIM seems to be higher than the incidence found in the literature, which could be explained by the chemotherapy regimen.<sup>29,30</sup> In fact, 71.1% of our patients received chemotherapy with FEC (5-fluorouracil, epirubicin, and cyclophosphamide), and Berlière et al found

**Figure 4** Hormone Measurements. A, AMH Serum Level Variation Between Inclusion and the End of Chemotherapy: Mean ( $\pm 95\%$  Confidence Intervals); B, Correlation Between Patient's Age and Their Pre-Treatment AMH Level. “\*\*” Indicates a Significant Difference ( $P \leq .05$ ) Between CIM and Non-CIM Patients



Abbreviations: AMH = anti-Müllerian hormone; CIM = chemotherapy-induced menopause.

approximately the same incidence of long-term amenorrhea with FEC-based chemotherapy.<sup>31</sup>

In line with previous studies, age was the main risk factor of CIM; older women have higher risk to become menopausal.<sup>30,32,33</sup> According to Wallace and Kesley, ovarian reserve declines with age, and only 3% remains at age 40. Therefore, among older patients, the risk of long-term amenorrhea or early menopause is greater.<sup>34</sup> This could explain the longer duration of amenorrhea for CIM women, and these results are consistent with findings by Peterk et al, which showed that: “older age is strongly related to decreased menstrual bleeding” in natural menopause as in chemotherapy-related premature menopause.<sup>35</sup>

However, the global fertility preservation rate was not important (12%); it was higher in non-CIM patients than in CIM patients, which could be explained by their younger age. Of course, younger women could be more interested in future pregnancy and, as a consequence, they could be more worried about pregnancy problems

than older women. In contrast, our study underlines that younger women more often recover menstruation and are less at risk of premature menopause, so fertility preservation should be ideally discussed with older patients (over 40 years) desiring to have children.<sup>36</sup>

In our analysis, CIM patients seemed to have shorter menstruation cycles than non-CIM patients. Apart from studies defining the menopause, the association between short menstruation cycles and menopause was not previously evidenced in patients with breast cancer treated by chemotherapy.<sup>11,37</sup> As defined by the WHO in 1996,<sup>11</sup> the length of menstrual cycle becomes shorter when women are closer to menopause; we can deduce that this information could also be predictive of menopause in our patients.

Concerning the number of chemotherapy cycles, non-CIM patients received, on average, 1 more chemotherapy cycle before the onset of amenorrhea, which means that amenorrhea appeared later in younger women, as shown by Bines et al.<sup>38</sup> This earlier onset of amenorrhea could be explained by a diminished stock of ovarian

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follicles in older women, in this case, the CIM patients.<sup>35</sup> According to our results, older age, short menstruation cycle, and faster amenorrhea could be predictive factors of longer CIA or premature menopause in young patients with breast cancer treated by chemotherapy.

The QoL assessment focused on functional part (QLQ-C30 and QLQ-BR23) and climacteric symptoms (Kupperman Index). It showed significantly impaired QoL shortly after chemotherapy in both groups of patients. This time effect concerned the 3 questionnaires (QLQ-C30, QLQ-BR23, and the Kupperman Index), showing that chemotherapy was damaging for the patients' QoL. These results are consistent with other studies and reviews demonstrating the negative effect of chemotherapy or other anticancer treatments on patients' QoL.<sup>39-41</sup> Scores obtained at 6 months post-chemotherapy on the QLQ-C30 and QLQ-BR23 measures, however, exhibit a tendency to return to baseline levels, showing that many consequences of chemotherapy on QoL were reversible and lasted only for a short period of time.<sup>41</sup> Before and/or after chemotherapy, all patients underwent other anticancer treatments such as surgery, radiotherapy, and hormone therapy, which could also impact the patients' QoL. Despite this, QoL scores were lower at the end of chemotherapy, suggesting that chemotherapy should have more negative impact than other treatments.

Concerning the main objective (QLQ-C30 functional score), which evaluates the functional part of general QoL in patients with cancer, no difference was evidenced between CIM and non-CIM patients. The score variation was quite similar, showing that the functional part of general QoL was not affected by the CIM. This preliminary data failed to reach the same difference as the STIC RMI study (5 points lesser in menopausal women). In contrast, between inclusion and 6 months post-chemotherapy, the functional score of QLQ-BR23 decreased stronger in CIM patients than in non-CIM patients, showing an impaired QoL. A difference of 13 points was also reported between them at 6 months post-chemotherapy, so the difference of 5 points was reached for this questionnaire. Even though these results did not reach significance, they underline a negative impact of menopause or CIM on patients QoL. The QLQ-BR23 questionnaire addresses specific issues of breast cancer such as body image and sexuality, whereas QLQ-C30 is more general. The QLQ-BR23 seemed to be more precise and more adequate to evaluate the patients' QoL in particular in our study. At this point of the study, we cannot conclude on the real incidence of CIM or its effect on functional QoL, but the results showed that long-term CIA has a tendency, with time, to damage the functional dimension of patients' QoL measured by the QLQ-BR23. We can expect that with the inclusion of the next 177 patients and a longer follow-up (30 months post-chemotherapy), differences will reach significance, and we will be able to confirm our hypotheses. The Kupperman Index evaluates the climacteric symptoms. At the end of chemotherapy, all patients experienced increase of these symptoms, but only CIM patients continuously reported the symptoms at 6 months post-chemotherapy. CIM negatively impacted the patients' mood, hot flushes, and vaginal dryness. The Kupperman Index confirmed that CIM patients were closer to postmenopausal status than non-CIM patients, and the differentiation based on amenorrhea duration seems to be a good marker.

Concerning hormonal variations, our data showed that the overall serum AMH and estradiol levels decreased after chemotherapy, whereas serum FSH levels increased, confirming the cytotoxic effect of chemotherapy on ovarian function.<sup>8,11,41</sup> As in other studies, a marked difference for AMH and FSH levels between inclusion and the end of chemotherapy was shown, but in our study, this difference was also significant for estradiol.<sup>41-43</sup> The comparison of these previous studies with our data showed that the numbers of patients included was smaller than in our study: the greater power here could explain why the difference reached significance for estradiol variations.

The initial AMH serum level was different between the 2 groups of patients, with a higher level in non-CIM patients: this shows that low pre-treatment AMH level is linked to long-term amenorrhea.<sup>43</sup> In contrast, the level after chemotherapy was mainly under the detection threshold for both groups of patients without any difference between them. As shown by other previous studies, the AMH level at the end of chemotherapy is at its lowest, and many patients have an undetectable level, which is consistent with our data.<sup>42-44</sup> Concerning AMH serum variation between inclusion and the end of chemotherapy, a significant difference was shown between the 2 groups, with a greater decrease among younger patients, which can be attributed to the difference found at baseline. On the other hand, a strong correlation between age and initial AMH level was evidenced, which correlates with the high level of AMH in non-CIM patients (younger patients). As shown by Anders et al and Henry et al, this data suggests that the initial AMH serum level, in association with age, may play a role in the prediction of ovarian function.<sup>43,45</sup> Although the prediction of CIM could help to determine the appropriate endocrine therapy when needed, further studies with larger cohort are needed to confirm these results. The final analysis of our study (with a total of 240 patients) will be much more informative on this issue. In addition, initial FSH levels tended to differ between CIM and non-CIM patients, with a high level in CIM patients. Basal FSH level could also contribute to predict CIM on young patients.

### Limitations

This interim analysis has some limitations, especially the small power owing to a small sample size. Concerning AMH, it would have been more interesting to continue the measurements during the follow-up, but we could not do this because of the considerable cost. Another limitation we should mention is the absence of transvaginal ultrasound performed before and after chemotherapy, which would have strengthened the data about the ovarian reserve with the ovarian volume calculation and the antra follicles count.

### Conclusions

This analysis suggests that the study is technically feasible with a good inclusion rate and sufficient data. Preliminary results did not evidence any difference between CIM and non-CIM patients for our main objective (impact of CIM on functional score of QLQ-C30). In contrast, we were able to point out that CIM patients' specific QoL (evaluated by the QLQ-BR23) is more impacted than non-CIM patients, and they experienced more climacteric symptoms as expected. According to this result, QLQ-BR23 seems to be more appropriate to evaluate the QoL changes in young patients

with breast cancer. Our results also underline that amenorrhea  $\geq 12$  months is linked to certain parameters: older age, low baseline AMH, high baseline FSH, shorter menstruation cycles, and earlier onset of amenorrhea. In particular, initial AMH level seems to be more informative regarding the risk of CIM when compared with FSH and/or estradiol. But these data are still insufficient to determine pre-treatment AMH level as a predictive factor of CIM, and additional prospective studies are needed on this issue. We also expect the final analysis with more patients (240 planned) and a longer follow-up (30 months post-chemotherapy) to be more precise on issues we have discussed herein.

### Clinical Practice Points

- Menopausal status is difficult to predict in young patients with breast cancer treated with chemotherapy. Moreover, chemotherapy is known to impair the patients' QoL, but the specific case of young women experiencing CIM lacks knowledge.
- Our preliminary results suggest, as expected, that age is predictive of menopause. Other parameters, like pre-treatment AMH level, in association with pre-treatment FSH level, shorter menstruation cycle, and earlier amenorrhea, seem also to be predictive of menopause in young women treated with chemotherapy. Additional prospective studies are needed to confirm these results. The EORTC QLQ-BR23 seems to be more precise to evaluate the QoL than the EORTC QLQ-C30, and it tends to show an impaired QoL in menopausal patients (at 6 months post-chemotherapy), which have to be confirmed in a larger cohort.
- Clearly identifying menopausal status of young patients with breast cancer could be helpful to determine the appropriate treatment, especially hormone therapy. Concerning the QoL, supportive care could be given to young patients experiencing CIM in order to improve their QoL.

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The authors have stated that they have no conflicts of interest.

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