IJC
International Journal of Cancer

Efficacy of anastrozole after tamoxifen in early breast cancer patients with chemotherapy-induced ovarian function failure

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The DATA study (NCT00301457) compared 6 and 3 years of anastrozole in postmenopausal women with hormone receptor-positive early breast cancer after 2–3 years of tamoxifen. Patients with chemotherapy-induced ovarian function failure (CIOFF) were also eligible, but could be at risk of ovarian function recovery (OFR). The current analysis compared the survival of women with CIOFF with definitely postmenopausal women and examined the influence of OFR on survival. Therefore, we selected patients from the DATA study aged 45–57 years at randomization who had received (neo)adjuvant chemotherapy. They were classified by reversibility of postmenopausal status: possibly reversible in case of CIOFF (n = 395) *versus* definitely postmenopausal (n = 261). The former were monitored by E2 measurements for OFR. The occurrence of OFR was incorporated as a time-dependent covariate in a Cox-regression model for calculating the hazard ratio (HR). We used the landmark method to calculate residual 5-year survival rates. When comparing CIOFF women with definitely postmenopausal women, the survival was not different. Among CIOFF women with available E2 follow-up values (n = 329), experiencing OFR (n = 39) had an unfavorable impact on distant recurrence-free survival (HR 2.27 [95% confidence interval [CI] 0.98–5.25; p = 0.05] and overall survival (HR 2.61 [95% CI 1.11–6.13; p = 0.03]). After adjusting for tumor features, the HRs became 2.11 (95% CI 0.89–5.02; p = 0.09) and 2.24 (95% CI 0.92–5.45; p = 0.07), respectively. The residual 5-year rate for distant recurrence-free survival was 76.9% for women with OFR and 92.1% for women without OFR, and for 5-year overall survival 80.8% and 94.4%, respectively. Women with CIOFF receiving anastrozole may be at increased risk of disease recurrence if experiencing OFR.

Key words: breast cancer, aromatase inhibitor, chemotherapy-induced amenorrhea, chemotherapy-induced ovarian function failure (CIOFF), ovarian function recovery (OFR)
Grant sponsor: AstraZeneca
[Correction added March 23, 2019 after first online publication: Figure 2 was updated.]
DOI: 10.1002/ijc.32093

History: Received 18 Apr 2018; Accepted 28 Nov 2018; Online 26 Dec 2018
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What's new?

In postmenopausal women with hormone receptor-positive breast cancer, aromatase inhibitors (AIs) can prevent disease recurrence and improve survival better than tamoxifen. However, AI-monotherapy should not be used in premenopausal women, as it can stimulate the estradiol production. Here, the authors investigated the effect of the AI anastrozole after prior tamoxifen in women with chemotherapy-induced ovarian function failure (CIOFF) *versus* postmenopausal women. The Survival was comparable for definitely postmenopausal women and those with CIOFF. However, women with CIOFF whose ovarian function returned had a poorer survival, despite regular monitoring of the estradiol levels.

Introduction

Aromatase inhibitors (AIs) are used as adjuvant therapy for postmenopausal breast cancer patients with hormone receptor-positive breast cancer.[1] By inhibiting the aromatase enzyme, they prevent the conversion from androgens to estradiol (E2) leading to E2 deprivation in postmenopausal women and thereby possibly preventing tumor cell growth if still present. In premenopausal women, AIs stimulate the gonadotropin secretion by inducing feedback stimulation of the hypothalamus–pituitary–ovary axis, resulting in a strong rise of the E2 level.[2] Consequently, AI-monotherapy is contraindicated in premenopausal breast cancer patients.[3,4] However, in postmenopausal women, AIs have been shown to be more efficient than tamoxifen in preventing disease recurrence and improving survival.[5]

In common practice, the menopausal status is not always easy to determine, causing AIs to be used in patients with chemotherapy-induced ovarian function failure (CIOFF) while little is known about the efficacy of AIs in this subgroup of women who are at risk of ovarian function recovery (OFR).[4,6,7]

The phase III DATA study assesses the impact of different durations of adjuvant anastrozole on survival after prior tamoxifen in postmenopausal women with hormone receptor-positive early breast cancer.[8] Women with CIOFF were also eligible. A recent analysis of the DATA study showed biochemical OFR in 12.4% of women with CIOFF at 30 months after randomization.[9] Furthermore, the E2 levels of these OFR patients were significantly higher during anastrozole treatment, even before developing OFR, in comparison to those who remained postmenopausal.[9] As a consequence, patients who experienced OFR may have received inefficient anticancer treatment and thereby a worse outcome. Therefore, in the current substudy, we analyzed the survival of women with CIOFF receiving adjuvant treatment with anastrozole for early breast cancer, and the impact of OFR on survival.

Methods

Study design and participants

This was an unplanned substudy from the open-label multicenter phase III randomized DATA trial, investigating the efficacy and safety of 6 *versus* 3 years of adjuvant anastrozole after 2–3 years of tamoxifen in postmenopausal, hormone receptor-positive early breast cancer patients.[8] The randomization procedure took place after 2–3 years of tamoxifen and before the initiation of adjuvant anastrozole. The study was conducted in the Netherlands by the Dutch Breast Cancer Research Group (BOOG) and included 1,860 eligible patients from 2006 until 2009. The protocol is available online (NCT00301457).

For the current substudy, we identified patients aged 45–57 years at randomization who had received (neo)adjuvant chemotherapy. The patient selection was described into more detail in an earlier publication.[9] Women who used gonadotropin releasing hormone (GnRH) agonists before randomization or had no postmenopausal E2 or FSH levels at randomization were excluded. We classified the patients in two main groups regardless of anastrozole assignment: (*i*) patients who had their last menstrual bleeding more than 1 year before chemotherapy administration or underwent a bilateral ovariectomy before randomization (definitely postmenopausal), and (*ii*) patients with CIOFF. Patients were considered having CIOFF if they had their last menstrual bleeding less than 1 year before administration of chemotherapy and had postmenopausal E2 and FSH levels at randomization according to local reference values in the participating hospitals. CIOFF women of whom follow-up information on E2 levels was available were followed for the occurrence of OFR. OFR was considered if any of the following events occurred: (*i*) return of menstrual bleeding and/or (*ii*) E2 levels not corresponding with postmenopausal levels according to local reference values. These E2 levels were monitored at 6-monthly intervals for 30 months after randomization. The physicians in the local hospitals decided on any treatment adjustments in case OFR was observed, either by adding ovarian function suppression (GnRH agonist, ovariectomy) or switching to tamoxifen. OFR and menstrual bleeding were reported as adverse events.

Objectives

The primary objective of our study was to compare disease-free survival, distant recurrence-free survival and overall survival between patients with CIOFF and those definitely postmenopausal. Second, we aimed to analyze the impact of OFR on survival in CIOFF patients with available follow-up E2 measurements. Events ending a period of disease-free survival included (non)invasive breast cancer recurrences (local, regional and distant), second primary (non)invasive (breast) cancer other than basal-cell or squamous-cell carcinoma of the skin or carcinoma *in situ* of the cervix and death of any cause.[10] Events ending a period of distant recurrence-

free survival were distant recurrence and death due to any cause.[10] Overall survival was defined as the interval between randomization and death from any cause.[10]

Statistical analysis

Survival curves were estimated with the Kaplan-Meier method in which time was censored at the date of last follow-up. We compared the survival of CIOFF patients with definitely postmenopausal women by using the log-rank test. The 5-year survival rates were calculated starting at randomization. About 42% of the women included in the DATA study were aged 60 years and above.[8] Of note, to overcome the influence of age (and its associated comorbidities) on survival in the analyses, we selected only those definitely postmenopausal patients who were within the same range of age (45–57 years) as the women with CIOFF. For the second research objective, we examined the influence of OFR, occurring at any time during the 30 months at which the E2 level was monitored, on survival in CIOFF women with a Cox proportional hazards model for calculating the hazard ratio (HR), with OFR as a time-dependent covariate. In addition, for graphical representation, the landmark method was used to assess the survival after a particular point in time, the so-called residual survival.[11] As we were interested to learn about the impact of OFR on survival, we chose 12 months after randomization as a landmark because the risk on OFR is highest in the first year after the start of anastrozole. The survival of patients who experienced OFR in the first year was plotted together with the survival of those not experiencing OFR in the first year. Consequently, patients who already had a survival event at that point in time were excluded for the residual survival curves. Those still at risk for an event after 12 months were included in the Kaplan-Meier survival curves and the 5-year residual survival rates.

Cox proportional hazards regression analysis was used to estimate HRs and 95% confidence intervals (CIs). Because of the inherently strong biological association between age and OFR, we decided not to correct our survival analyses for age to avoid multicollinearity. The worse prognosis of tumors at a younger age will be reflected in more aggressive tumor features (tumor size, nodal status, tumor grade and hormone receptor status), for which we adjusted the HRs in a multivariable analysis. The reported *p*-values were calculated with Wald tests. All reported *p*-values are two-sided and a *p*-value ≤0.05 was considered statistically significant. All analyses were performed using SAS version 9.2.

Results

Patient characteristics

Of the 1860 randomized DATA patients, 790 were 45–57 years at randomization and had received (neo)adjuvant chemotherapy. Of these, 261 women were considered definitely postmenopausal and 395 were considered to have CIOFF, of whom 39 experienced OFR and 290 did not. Of 66 patients, it remained unknown whether they experienced OFR as no follow-up E2 levels were available. Another 134 patients were not eligible for this substudy because they used GnRH agonists before randomization or had no postmenopausal E2 or FSH levels available at randomization. Figure 1 presents the flow chart on the patient selection.

Table 1 presents the baseline characteristics of the groups. Between the CIOFF and definitely postmenopausal groups there were clinically small but statistically significant differences regarding nodal involvement ($p = 0.02$), histological grade ($p = 0.01$), estrogen/progesterone receptor status ($p = 0.04$) and body mass index ($p = 0.01$). The median age of both groups was 51.0 years (range, 45.0–57.0).

Among the patients with CIOFF, the 30-month rate of OFR was 5.1% for patients age 50 and above ($n = 209$), *versus* 25.2% for patients younger than age 50 ($n = 120$), as reported previously.[9] Patients with OFR ($n = 39$) were younger than those without OFR (median age 48.0 years [range, 45.0–54.0] *versus* 51.0 years [range, 45.0–57.0]) ($p \leq 0.0001$). Other than age, there were no differences between the OFR and no-OFR groups. Of the 39 OFR patients, 19 (48.7%) reported menstrual bleeding.[9] In 27 (69.2%) patients experiencing OFR, adjuvant endocrine treatment was adjusted by adding a GnRH agonist (with or without an AI) ($n = 14$), switching to tamoxifen ($n = 6$) or performing a bilateral ovariectomy ($n = 7$), as previously reported.[9] In all OFR patients with a breast cancer recurrence, the endocrine treatment had been adjusted.

CIOFF *versus* definitely postmenopausal patients

After a median follow-up of 7.3 years after randomization ($P_5 = 5.9$, $P_{95} = 9.0$), the 5-year rate for disease-free survival was not statistically significantly different between women with CIOFF and definitely postmenopausal women (86.8% and 85.4%, respectively; HR 0.79, 95% CI 0.55–1.12; $p = 0.18$). The 5-year rates of distant recurrence-free survival (90.6% *versus* 88.8%, HR 0.77, 95% CI 0.50–1.18; $p = 0.22$) and overall survival (93.4% *versus* 90.7%, HR 0.87, 95% CI 0.54–1.41; $p = 0.58$) were also not statistically significantly different. Table 2 presents the incidence of the efficacy endpoint events. The survival curves are presented in Figure 2. After adjustment for tumor size, nodal status, tumor grade and hormone receptor status, the HRs changed only marginally (Table 3).

Impact of OFR on survival

The disease-free survival for patients experiencing OFR ($n = 39$) was not different in comparison to patients without OFR ($n = 290$) (HR 1.45, 95% CI 0.68–3.11; $p = 0.34$). However, experiencing OFR was associated with an increased risk of distant recurrence (HR 2.27, 95% CI 0.98–5.25; $p = 0.05$) and a reduced overall survival (HR 2.61, 95% CI 1.11–6.13; $p = 0.03$). The HR and 95% CI after adjusting for tumor size, nodal status, tumor grade and hormone receptor status changed only slightly but became statistically nonsignificant

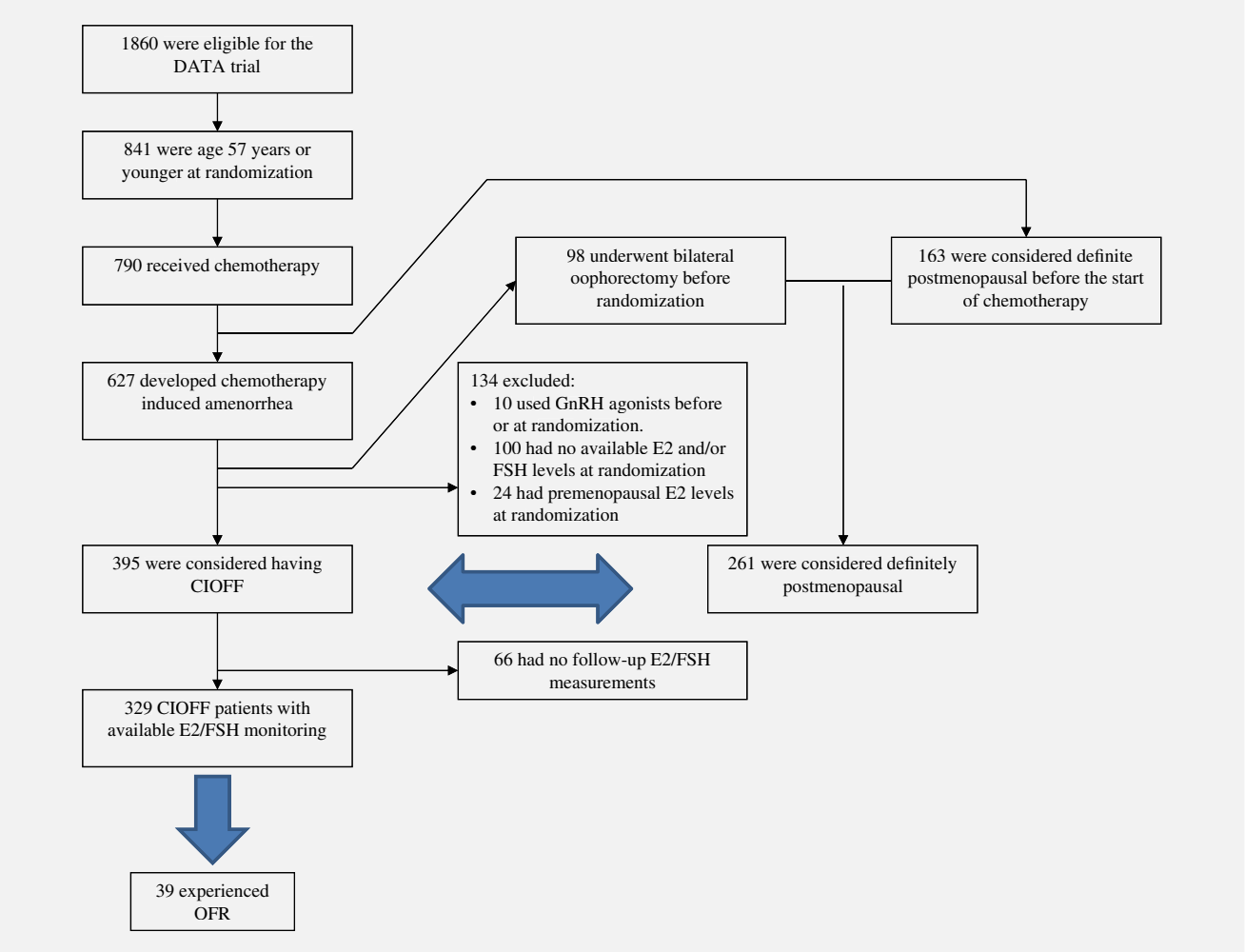

Figure 1. Flowchart of the patient selection out of the DATA study. CIOFF, chemotherapy-induced ovarian function failure. [Color figure can be viewed at wileyonlinelibrary.com]

(HR 2.11 [95% CI 0.89–5.02; p = 0.09] and 2.24 [95% CI 0.92–5.45; p = 0.07], respectively) (Table 3). The survival curves are presented in Figure 3.

The 5-year residual survival rates for patients experiencing OFR in the first year after randomization (n = 26) in comparison to women without OFR were for disease-free survival 73.1% *versus* 87.4%, for distant recurrence-free survival 76.9% *versus* 92.1% and for overall survival 80.8% and 94.4%. The Kaplan-Meier curves for these outcome measures after a landmark of 1 year are presented in Figure 2.

Discussion

This is the first study in a large study population of 329 hormone receptor-positive early breast cancer patients with CIOFF showing that experiencing OFR during treatment with adjuvant anastrozole was associated with an increased risk of distant disease-recurrence and a reduced overall survival. The negative impact of OFR on breast cancer survival during adjuvant anastrozole treatment was observed despite regular E2 monitoring at 6-monthly intervals and adjusting endocrine treatment at OFR detection.

So far, only one other study reported on the impact of OFR in women using AIs.[4] In that study, 17 out of 53 (32%) patients with chemotherapy-induced amenorrhea developed OFR during exemestane therapy after prior tamoxifen. At detection of OFR, exemestane was replaced by tamoxifen. Despite treatment adjustment, OFR resulted in a worse disease-free survival (HR 9.3, 95% CI 3.3–48.0; p = 0.04) compared to the women without OFR. A possible explanation for these findings and those of our study is the existence of an increased E2 level before OFR detection and treatment adjustment. In our study this period was maximally 6 months. It is generally advised to monitor E2 levels during AI therapy every 3 months for at least 2 years.[12] Nevertheless, we believe our results show that strict monitoring is not safe either.

A meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that the administration of an LHRH-agonist as adjuvant treatment in addition to

Table 1. Baseline characteristics of the patients included in our study

	CIOFF total group *N* = 395	Definitely postmenopausal *N* = 261	*CIOFF SUBGROUPS*	
			CIOFF with OFR *N* = 39	CIOFF without OFR *N* = 290
Age at randomization (median, range)	51.0 (45.0–57.0)	51.0 (45.0–57.0)	48.0 (45.0–54.0)	51.0 (45.0–57.0)
45–50 years – no. (%)	134 (33.9)	89 (34.1)	28 (71.8)	92 (31.7)
≥ 50 years – no. (%)	261 (66.1)	172 (65.9)	11 (28.2)	198 (68.3)
Tumor status – no. (%)				
pT1	165 (41.8)	106 (40.6)	15 (38.5)	122 (42.1)
pT2	181 (45.8)	129 (49.4)	20 (51.3)	136 (46.9)
pT3/4	49 (12.4)	26 (10.0)	4 (10.3)	32 (11.0)
Nodal status – no. (%)				
pN0 / pN0(i+)	102 (25.8)	94 (36.0)	13 (33.3)	76 (26.2)
pN1	230 (58.2)	136 (52.1)	21 (53.9)	171 (59.0)
pN2 / pN3	63 (16.0)	31 (11.9)	5 (12.8)	43 (14.8)
Histological grade – no. (%)				
Grade I	72 (18.2)	33 (12.6)	4 (10.3)	55 (19.0)
Grade II	213 (53.9)	124 (47.5)	19 (48.7)	157 (54.1)
Grade III	100 (25.3)	96 (36.8)	15 (38.5)	72 (24.8)
Unknown	10 (2.5)	8 (3.1)	1 (2.6)	6 (2.1)
Hormone receptor status – no. (%)				
ER-positive/PgR-positive	323 (81.8)	192 (73.6)	32 (82.1)	241 (83.1)
ER-positive/PgR-negative/unknown	63 (16.0)	59 (22.6)	5 (12.8)	43 (14.8)
ER-negative/PgR-positive	9 (2.3)	10 (3.8)	2 (5.1)	6 (2.1)
HER2 status – no. (%)				
Negative	382 (96.7)	257 (98.5)	39 (100)	279 (96.2)
Positive	10 (2.5)	4 (1.5)	0 (0.0)	8 (2.8)
Unknown	3 (0.8)	0 (0.0)	0 (0.0)	3 (1.0)
Type of breast surgery – no. (%)				
Breast-conserving surgery	188 (47.6)	131 (50.2)	19 (48.7)	140 (48.3)
Mastectomy	207 (52.4)	130 (49.8)	20 (51.3)	150 (51.7)
Type of axillary surgery – no. (%)				
Sentinel node only	129 (32.7)	80 (30.7)	9 (23.1)	89 (30.7)
Sentinel node plus axillary lymph node dissection	187 (47.3)	115 (44.1)	21 (53.6)	141 (48.6)
Axillary lymph node dissection	78 (19.7)	63 (24.1)	9 (23.1)	59 (20.3)
None	1 (0.3)	3 (1.1)	0 (0.0)	1 (0.3)
Radiotherapy – no. (%)				
Local and regional lymph nodes	167 (42.3)	103 (39.5)	19 (48.7)	113 (39.0)
Local	103 (26.1)	76 (29.1)	7 (17.9)	79 (27.2)
Regional	6 (1.5)	4 (1.5)	0 (0.0)	5 (1.7)
None/unknown	119 (30.1)	78 (29.9)	13 (33.3)	93 (32.1)
Prior (neo)adjuvant chemotherapy – no. (%)				
Anthracycline- and taxane-containing regimen	47 (11.9)	27 (10.4)	4 (10.3)	38 (13.1)
Anthracycline-containing regimen without taxane	332 (84.1)	230 (88.1)	34 (87.2)	239 (82.4)
Taxane without antracycline	2 (0.5)	1 (0.4)	0 (0.0)	1 (0.3)
Regimen without anthracycline or taxane	2 (0.5)	3 (1.2)	1 (2.6)	12 (4.1)
Prior HER2-targeted therapy – no. (%)				
Yes	14 (3.5)	2 (0.7)	0 (0.0)	2 (0.7)
Previous duration of tamoxifen – no. (%)				
≤ 2.5 years	276 (69.9)	183 (70.1)	28 (71.8)	201 (69.3)
›2.5 years	119 (30.1)	78 (30.0)	11 (28.2)	89 (30.7)

(Continues)

Table 1. Baseline characteristics of the patients included in our study (Continued)

	CIOFF total group *N* = 395	Definitely postmenopausal *N* = 261	*CIOFF SUBGROUPS*	
			CIOFF with OFR *N* = 39	CIOFF without OFR *N* = 290
Body Mass Index (kg/m^2) (median, range)	24.9 (14.5–52.0)	26.1 (19.1–60.2)	24.0 (19.1–36.1)	25.1 (1.45–52.0)
‹25.0–no. (%)	194 (49.1)	101 (38.7)	23 (59.0)	137 (47.2)
25.0–29.9	127 (32.2)	104 (39.8)	14 (35.9)	95 (32.8)
›30.0	60 (15.2)	49 (18.8)	2 (5.1)	46 (15.9)
Missing	14 (3.5)	7 (2.7)	0 (0.0)	12 (4.1)

Of 66 patients, no follow-up E2 levels were available. Therefore, it was not possible to determine if they had experienced OFR.
Abbreviations: CIOFF, chemotherapy-induced ovarian function failure; OFR, ovarian function recovery.

chemotherapy, with or without tamoxifen, reduced the risk of breast cancer recurrence by 12.7% (95% CI 2.4–21.9; $p = 0.02$), death after recurrence by 15.1% (95% CI 1.8–26.7; $p = 0.03$) and overall survival by 13.6% (95% CI 0.6–24.9; $p = 0.04$).[13] In the NSABP-B30 study, concerning women with estrogen receptor-positive breast cancer receiving tamoxifen as adjuvant endocrine treatment, those with chemotherapy-induced amenorrhea for at least 6 months had a better disease-free survival (HR 0.51, $p < 0.001$) and overall survival (HR 0.52, $p = 0.002$) in comparison to women who did not experience amenorrhea or regained their menstrual cycles within 6 months.[14,15] The Suppression of Ovarian Function Trial (SOFT) also showed an improved rate of disease-free survival and overall survival when adding ovarian function suppression to tamoxifen as compared to tamoxifen alone in premenopausal women who were at sufficient risk for recurrence to warrant adjuvant chemotherapy.[16] In our opinion, these results demonstrate that ovarian function suppression improves breast cancer outcome of women with hormone receptor-positive breast cancer treated with tamoxifen. Hence, a dual endocrine treatment is more effective than a single one.

However, a totally different situation exists for the use of AIs. Because of its working mechanism, absence of ovarian

Table 2. Incidence of the efficacy end point events

	CIOFF *N* = 395	Definitely postmenopausal *N* = 261	CIOFF with OFR *N* = 39	CIOFF without OFR *N* = 290
Primary end point –no. (%)				
Disease-free survival event[1]	85	71	11	51
Local recurrence	3 (3.5)	9 (12.7)	1 (9.1)	2 (3.9)
Regional recurrence	9 (10.6)	9 (12.7)	2 (18.2)	5 (9.8)
Distant recurrence[2]	38 (44.7)	25 (35.2)	6 (54.5)	23 (45.1)
Visceral	20 (23.5)	11 (15.5)	4 (36.4)	12 (23.5)
Bone	24 (28.2)	15 (21.1)	4 (36.4)	14 (27.5)
Soft tissue	3 (3.5)	1 (1.4)	1 (9.1)	2 (3.9)
Other	5 (5.9)	2 (2.8)	0 (0.0)	3 (5.9)
Second (noninvasive) breast cancer	11 (12.9)	9 (12.7)	1 (9.1)	8 (15.7)
Ipsilateral invasive breast cancer	1 (1.2)	1 (1.4)	0 (0.0)	1 (2.0)
Ipsilateral DCIS	0 (0.0)	2 (2.8)	0 (0.0)	0 (0.0)
Contralateral invasive breast cancer	7 (8.2)	4 (5.6)	0 (0.0)	5 (9.8)
Contralateral DCIS	3 (3.5)	2 (2.8)	1 (9.1)	2 (3.9)
Second, non-breast cancer	17 (20.0)	11 (15.5)	0 (0.0)	11 (21.6)
Death without prior breast cancer event	7 (8.2)	8 (11.3)	1 (9.1)	2 (3.9)
Secondary end points –no.				
Distant recurrence-free survival event[3]	47	39	7	26
Death from any cause	40	29	7	21

Of 66 patients, no follow-up E2 levels were available. Therefore, it was not possible to determine if they had experienced OFR.
[1]Patients may have had multiple disease-free survival events at the same moment.
[2]In some patients multiple locations of metastases were reported.
[3]The number of patients with a distant recurrence at any time during follow-up. Also the patients with a prior locoregional recurrence or second primary who developed a distant recurrence thereafter were reported.
Abbreviations: CIOFF, chemotherapy-induced ovarian function failure; OFR, ovarian function recovery. DCIS, ductal carcinoma in situ.

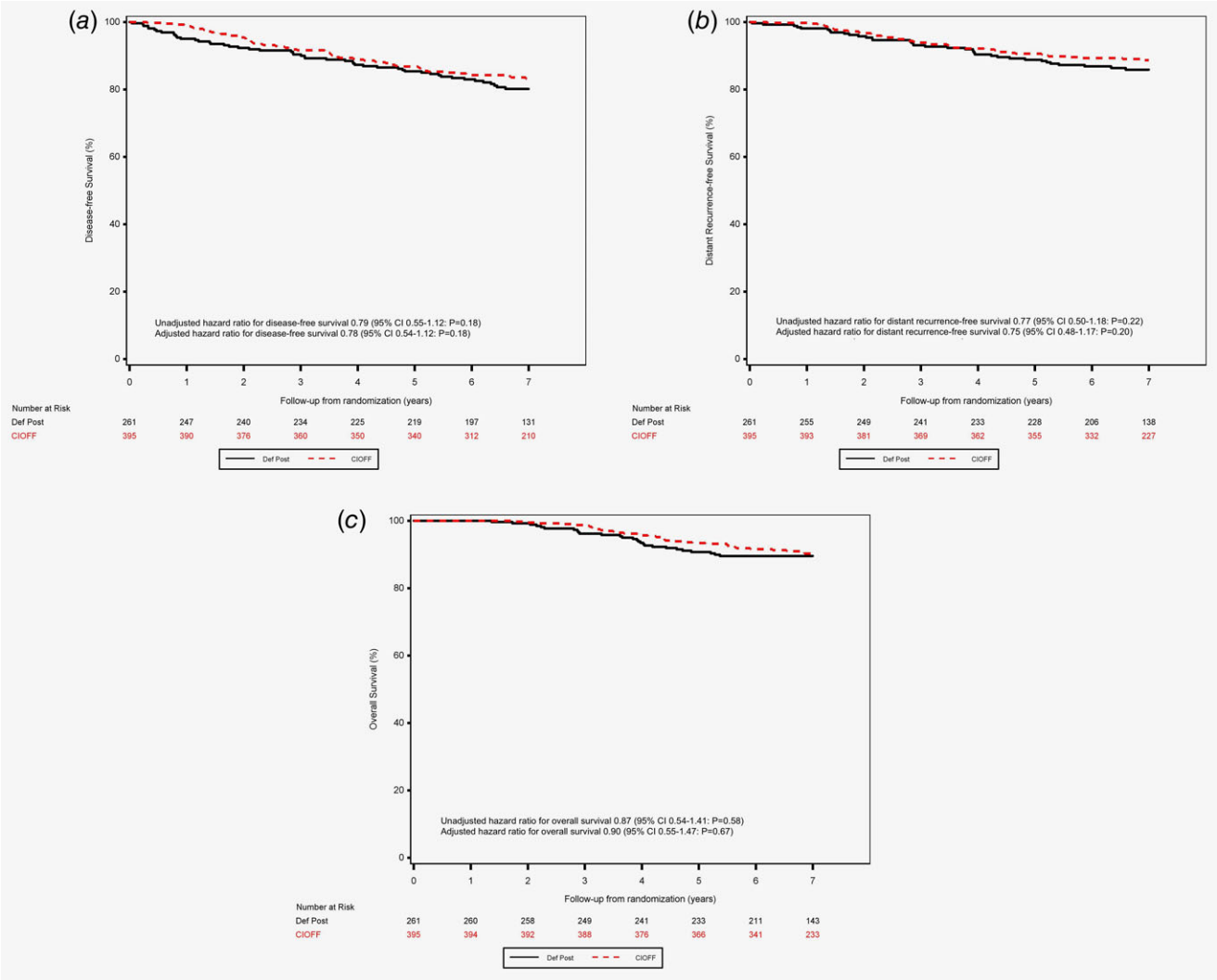

Figure 2. Survival curves for patients with chemotherapy-induced ovarian function failure (CIOFF) *versus* definitely postmenopausal women. (*a*) Disease-free survival, (*b*) distant recurrence-free survival and (*c*) overall survival. The adjusted hazard ratios were corrected for tumor size, nodal status, tumor grade, and hormone receptor status.

function, either naturally by postmenopausal status or by ovarian function suppression, is a pivotal condition for AIs to be effective. Therefore, if AIs are used in premenopausal patients, these two treatment modalities should always be combined. The logical next question is whether in the presence of ovarian function suppression, AIs are more effective than tamoxifen in women with ER-positive early breast cancer who were initially premenopausal.

In a combined analysis of the SOFT and Tamoxifen and Exemestane Trial (TEXT),[16] administration of exemestane plus ovarian suppression resulted in a statistically significantly improved disease-free survival when compared to tamoxifen monotherapy (HR 0.65, 95% CI 0.35–0.81) or the combination tamoxifen/GnRH agonist (HR 0.77, 95% CI 0.67–0.90) after a median follow-up of 8 years. However, the combined treatment with exemestane/GnRH agonist did not result in an improved overall survival (HR 0.79, 95% CI 0.57–1.09) when compared to tamoxifen monotherapy, neither when compared to the combination tamoxifen/GnRH agonist (HR 0.98, 95% CI 0.79–1.22).[16] The ABCSG-12 trial, studying the efficacy of anastrozole/GnRH agonist *versus* tamoxifen/GnRH agonist (without chemotherapy) in premenopausal early breast cancer patients, even found a worse overall survival for the former after a median follow-up of 5.2 years.[17] Yet, in randomized trials of adjuvant endocrine therapy, maximal separation of Kaplan-Meier curves for overall survival has typically occurred more than 10 years after randomization. Hence, these data regarding survival and late adverse events could be considered immature.[18,19]

The onset of menopause in Caucasian women is 51 years on average with a considerable variability; 5% of women above the age of 55 years and another 5% under the age of 45 years.[20] The supplementary figure S2A of the TEXT/SOFT trial manuscript

Table 3. The hazard ratio (HR) on an event when patients with CIOFF (n = 395) were compared with definitely postmenopausal women (n = 261). The HR on an event after OFR had been observed (n = 39) among the women with CIOFF.

	Disease-free survival			Distant recurrence-free survival			Overall survival		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
CIOFF *versus* definitely postmenopausal									
Unadjusted HR	0.79	0.55–1.12	0.18	0.77	0.50–1.18	0.22	0.87	0.54–1.41	0.58
HR after adjusting for tumor size, nodal status, tumor grade and hormone receptor status	0.78	0.54–1.12	0.18	0.75	0.48–1.17	0.20	0.90	0.55–1.47	0.67
Impact of OFR on survival among women with CIOFF									
Unadjusted HR	1.45	0.68–3.11	0.34	2.27	0.98–5.25	0.05	2.61	1.11–6.13	0.03
HR after adjusting for tumor size, nodal status, tumor grade and hormone receptor status	1.33	0.61–2.90	0.48	2.11	0.89–5.02	0.09	2.24	0.92–5.45	0.07

Abbreviations: CIOFF, chemotherapy-induced ovarian function failure; OFR, ovarian function recovery; 95% CI, 95% confidence interval.

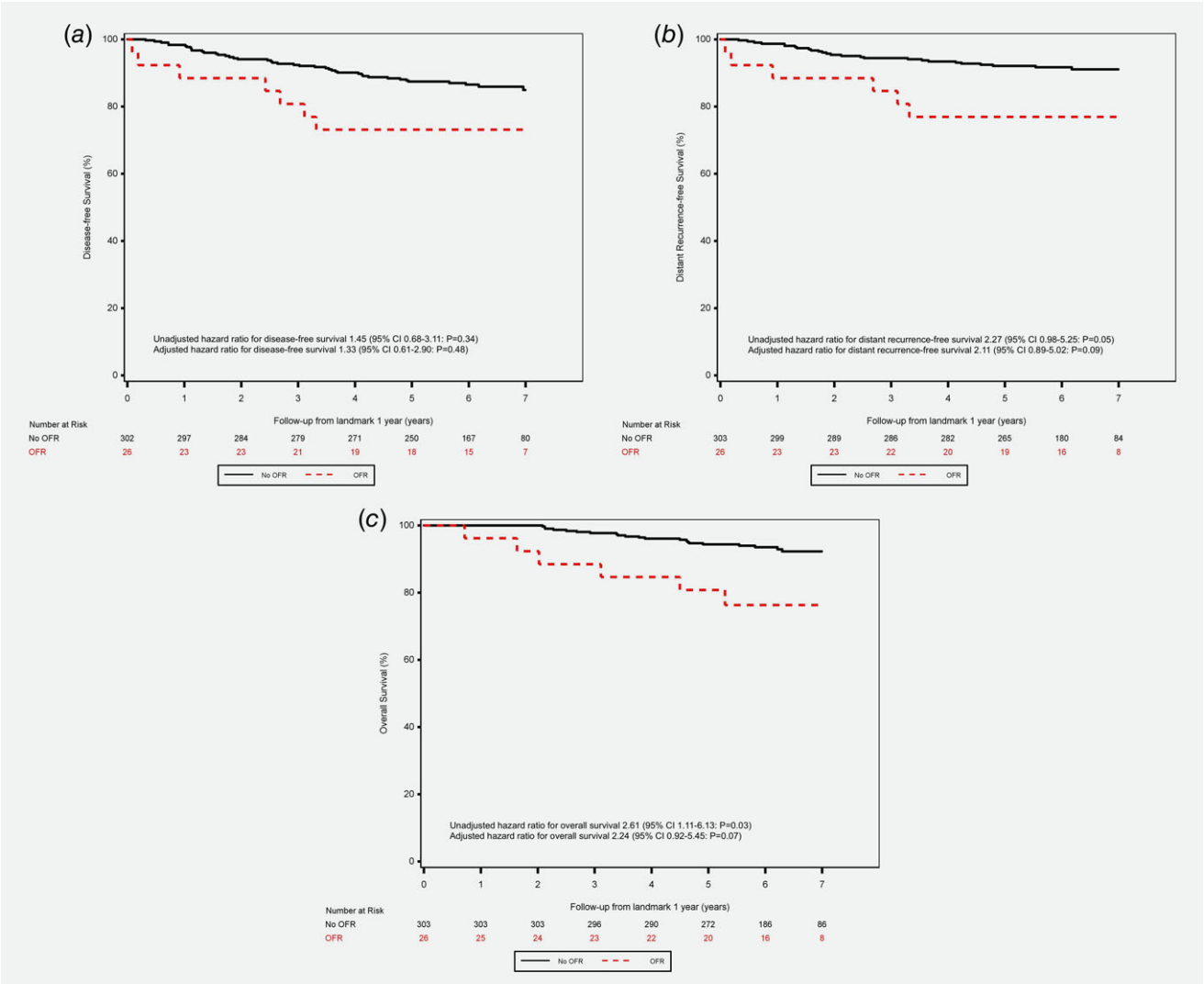

Figure 3. Residual survival curves for chemotherapy-induced ovarian function failure (CIOFF) patients experiencing ovarian function recovery (OFR) in the first year after randomization *versus* CIOFF patients who did not experience OFR. (*a*) Disease-free survival, (*b*) distant recurrence-free survival, and (*c*) overall survival. These panels show the residual survival curves from the **12**-month landmark analyses of the effect of OFR on survival. The adjusted hazard ratios were corrected for tumor size, nodal status, tumor grade, and hormone receptor status.

shows an HR for disease-free survival approaching 1.0 with increasing age from less than 35 to above 50 years when comparing tamoxifen plus ovarian function suppression with tamoxifen alone, indicating no added value of GnRH agonists to tamoxifen as natural menopause steps in.[16] On the contrary, supplementary figure S6 of the TEXT/SOFT analyses regarding the combination of exemestane with a GnRH agonist and the additional analyses in women under 35 years of age show, as illustrated by the HRs, a gradually increasing favorable impact on the disease-free survival with rising age for the combination AI/GnRH agonist in comparison to tamoxifen/GnRH agonist, possibly due to incomplete ovarian function suppression by GnRH agonists in younger patients.[16,21] As this was not observed in patients treated with tamoxifen, this cannot point at an independent prognostic value of age.[22] The incomplete ovarian function suppression by a GnRH agonist was indeed observed in the SOFT-EST trial,[23] where during 12 months of follow-up, 34.2% of the patients had inadequately suppressed (increased) E2 levels, at least once.

Considering that the results of the TEXT/SOFT trials might lead to an increased prescription of the combination treatment of GnRH agonist/AI in premenopausal patients in real life, we believe that the data of the SOFT-EST trial,[23] the ABCSG-12 trial[17], and our study show that the risk of incomplete ovarian function suppression—either by using GnRH agonists at a young age or by OFR in case of CIOFF—in the presence of AIs is clinically important with respect to overall outcome. Until further follow-up results of the TEXT/SOFT and ABCSG-12 trials will be available, we suggest cautiousness.

As OFR is characterized by high E2 levels, the findings of the current study raise another essential question; if increased E2 levels cause worse survival outcomes, does a more pronounced decrease of E2 levels lead to improved breast cancer survival? And if so, what should the target value be? Currently, only few data are known about the clinical consequences of the extent of E2 reduction during AI treatment. Letrozole has been shown to decrease plasma E2 levels to a greater extent in postmenopausal women with ER-positive breast cancer, in comparison to anastrozole.[24] Yet, the efficacy of letrozole regarding survival outcomes has not shown to be superior over anastrozole or exemestane.[25–27] Future research on the optimization of AI treatment should focus hereon by linking periodically measured E2 levels during AI treatment to survival outcomes to identify a so-called target value at which maximum efficacy is expected. Also the influence of BMI on the extent of E2 deprivation during AI treatment needs further investigation, as it has not been given by weight- or body-surface-area–related dosing: one standard dosage for all patients. This might explain the worse survival for obese women undergoing endocrine treatment found in several studies.[28–31]

As the performances of most E2 assays are modest and various tests are used in different laboratories, interpreting E2 levels can also be challenging.[32] Moreover, cross-reaction between E2 and metabolites of steroidal AIs can be problematic, even in specialized immunoassays.[33] Ultrasensitive assays incorporating tandem mass spectroscopy have been shown to be more sensitive at very low E2 concentrations in comparison to standard E2 assays.[34,35] However, agreement among mass spectrometry-based methods is also lacking.[36] Therefore, testing E2 levels during AI treatment with a mass spectrometry assay in a central laboratory might be valuable for a trial setting, but is not (yet) necessary/feasible for daily practice, the more since it was shown that both indirect and direct assays are accurate in determining the menopausal status.[4]

In our study the E2 levels were assessed at local laboratories, which may be considered a limitation. Furthermore, the current analysis was an unplanned substudy whereby confounding by indication could not fully be ruled out. A significant number of patients were excluded from our substudy due to the lack of E2 measurements. Nevertheless, our study concerns survival data on a large and quite homogeneous population with early breast cancer patients between 45 and 57 years, who all received prior chemotherapy and 2–3 years of tamoxifen before anastrozole initiation. However, as the number of patients with OFR after CIOFF was small, confirmation of our data in other patient sets would be very welcomed.

Conclusion

Hormone receptor-positive early breast cancer patients with CIOFF treated with anastrozole have comparable survival outcomes in comparison to women who are definitely postmenopausal. However, among the women with CIOFF, OFR had an unfavorable impact on the distant recurrence-free survival and overall survival. These data warrant further research for this group of patients.

Acknowledgements

The authors thank W. Lemmens and B. Schalk for their assistance with performing the statistical analyses.

Disclosures: I.E.G. van Hellemond and A.C.P. Swinkels received a research grant from AstraZeneca. M. de Boer received research grants from Roche, Novartis, Eisai, AstraZeneca and Pfizer. S.C. Linn reports advisory board membership for TBM Health, Novartis and Pfizer, and institutional unrestricted research grant and studying support from AstraZeneca, Roche, Genentech and Tesaro. V.C.G. Tjan-Heijnen received research grants from AstraZeneca, Novartis, Pfizer, Roche, Lily and Eisai.

Honorarium for lectures: Roche, Novartis, Pfizer and Lily. The other authors have no conflicts of interest to declare.

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