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ORIGINAL ARTICLE

Concurrent and sequential initiation of ovarian function suppression with chemotherapy in premenopausal women with endocrine-responsive early breast cancer: an exploratory analysis of TEXT and SOFT

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Background: Recent breast cancer treatment guidelines recommend that higher-risk premenopausal patients should receive ovarian function suppression (OFS) as part of adjuvant endocrine therapy. If chemotherapy is also given, it is uncertain whether to select concurrent or sequential OFS initiation.

Design and methods: We analyzed 1872 patients enrolled in the randomized phase III TEXT and SOFT trials who received adjuvant chemotherapy for hormone receptor-positive, HER2-negative breast cancer and upon randomization to an OFS-containing adjuvant endocrine therapy, initiated gonadotropin-releasing-hormone-agonist triptorelin. Breast cancer-free interval (BCFI) was compared between patients who received OFS concurrently with chemotherapy in TEXT ($n = 1242$) versus sequentially post-chemotherapy in SOFT ($n = 630$). Because timing of trial enrollment relative to adjuvant chemotherapy differed, we implemented landmark analysis re-defining BCFI beginning 1 year after final dose of chemotherapy (median, 15.5 and 8.1 months from enrollment to landmark in TEXT and SOFT, respectively). As a non-randomized treatment comparison, we implemented comparative-effectiveness propensity score methodology with weighted Cox modeling.

Results: Distributions of several clinico-pathologic characteristics differed between groups. Patients who were premenopausal post-chemotherapy in SOFT were younger on average. The median duration of adjuvant chemotherapy was 18 weeks in both groups. There were 231 (12%) BC events after post-landmark median follow-up of about 5 years. Concurrent use of triptorelin

with chemotherapy was not associated with a significant difference in post-landmark BCFI compared with sequential triptorelin post-chemotherapy, either in the overall population (HR = 1.11, 95% CI 0.72–1.72; $P = 0.72$; 4-year BCFI 89% in both groups), or in the subgroup of 692 women <40 years at diagnosis (HR = 1.13, 95% CI 0.69–1.84) who are less likely to develop chemotherapy-induced amenorrhea.

Conclusion: Based on comparative-effectiveness modeling of TEXT and SOFT after about 5 years median follow-up, with limited statistical power especially for the subgroup <40 years, neither detrimental nor beneficial effect of concurrent administration of OFS with chemotherapy on the efficacy of adjuvant therapy that includes chemotherapy was detected.

Clinicaltrials.gov: NCT00066690 and NCT00066703.

Key words: adjuvant therapy, GnRH-agonist, hormone receptor-positive, ovarian function suppression, premenopausal, triptorelin

Introduction

Surgical ovarian ablation was the first systemic adjuvant treatment of breast cancer [1]. More recently, gonadotropin-releasing-hormone (GnRH) agonists provide a reversible method to achieve ovarian function suppression (OFS). Several trials have since compared ovarian ablation or GnRH-agonist-induced OFS to chemotherapy alone and/or with chemotherapy followed by OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (with or without oral endocrine therapy) [2]. However, addition of OFS to endocrine adjuvant treatment of HR+ breast cancer has remained controversial for a number of reasons, including the confounding effect of chemotherapy-induced amenorrhea (CIA) and study designs including non-HR+ patients and omitting a tamoxifen-alone comparator. Current anthracycline/taxane-based regimens are associated with a lower incidence of CIA than older alkylating-based regimens such as cyclophosphamide/methotrexate/5-fluorouracil, especially in younger women [3]. Data from 9864 premenopausal patients treated with chemotherapy alone in cooperative group trials showed a significantly worse outcome for very young patients (<35 years) with HR+ tumors compared with older HR+ patients [4]. The age-related difference in outcome was much smaller for HR-negative patients. The lower incidence of CIA in very young patients translates into an attenuated endocrine effect of chemotherapy and suggests a potential impact of early initiation of adjuvant endocrine therapy [4, 5].

There are theoretical concerns about the concurrent use of endocrine therapy with chemotherapy based on laboratory and animal studies [6–8]. The only randomized evidence in the adjuvant setting derives from studies in postmenopausal women treated with tamoxifen [9–11]. The data for concurrent use of endocrine therapy and chemotherapy in premenopausal women are scanty: among 1096 patients (39% premenopausal) enrolled in two trials of adjuvant chemotherapy, in which tamoxifen was given concomitantly or sequentially by physician discretion, no difference in DFS was reported [12]. Subgroup analyses suggested greater benefit of concomitant versus sequential therapy among 427 premenopausal women, particularly those aged ≤40 years [12]. However, concomitant tamoxifen does increase the risk of thrombotic events during chemotherapy and is not recommended [11].

The TEXT and SOFT randomized phase III trials studied adjuvant endocrine therapy for premenopausal women with HR+ early breast cancer [13–15]. TEXT enrolled patients before starting any adjuvant therapy, including chemotherapy, whereas SOFT enrolled patients who were premenopausal after finishing adjuvant chemotherapy. Thus the timing of OFS and chemotherapy, if chemotherapy was given, differed in the two trials, being concurrent in TEXT and sequential in SOFT. Based largely on the results of SOFT and TEXT, guidelines recommend higher-risk patients should receive OFS as part of adjuvant endocrine therapy [16–19].

Several questions remain. Is there a best timing for initiating OFS when chemotherapy is also given? Is there a benefit to undergoing OFS as quickly as possible, concurrently with chemotherapy, or might concurrent administration be detrimental? Is it equivalent to wait and see if chemotherapy induces menopause thereby avoiding GnRH-agonist injections? Should age be taken into consideration when deciding when to start OFS? In the absence of a randomized clinical trial to address these questions, we used comparative-effectiveness methods for non-randomized treatment comparisons to conduct an exploratory, observational study of SOFT/TEXT patients treated with adjuvant chemotherapy and GnRH-agonist. We investigated whether there was evidence of differential efficacy between initiating adjuvant GnRH-agonist concurrently with chemotherapy versus sequentially after chemotherapy, once premenopausal status was reestablished.

Patients and methods

The designs and conduct of the TEXT/SOFT trials have been described previously [13–15]. The ethics committee at each participating center approved the study protocols; all patients provided written informed consent. In both trials, eligible premenopausal women had surgically resected, invasive early HR+ breast cancer (≥10% ER and/or PgR-expressing cells). Endocrine therapy, including OFS if it was assigned, was given for 5 years; oral endocrine therapy commenced after chemotherapy in both trials.

In TEXT, OFS was given from the start of adjuvant therapy. Between November 2003 and March 2011, 2660 women were randomized within 12 weeks after definitive surgery to exemestane + OFS or tamoxifen + OFS. OFS was by GnRH-agonist triptorelin; after at least 6 months of triptorelin, patients could opt for ovarian ablation. Chemotherapy was optional and planned for 1607 (60%) patients, started concurrently with triptorelin.

In SOFT, OFS was given sequentially after chemotherapy. Between December 2003 and January 2011, 3047 women were randomized to tamoxifen, tamoxifen + OFS or exemestane + OFS. A total of 1628 (53%) patients who received prior (neo)adjuvant chemotherapy were randomized within 8 months after the final dose of chemotherapy once a

premenopausal level of estradiol was confirmed. Use of triptorelin or ovarian ablation, if OFS was assigned, was by patient preference.

Analysis population, endpoints and statistical considerations

In the intention-to-treat populations, 2693 patients within the chemotherapy strata were randomized to an OFS-containing combination. After exclusions, 1320 patients from TEXT and 654 from SOFT with HER2-negative disease treated with adjuvant chemotherapy and triptorelin were analyzed (Figure 1). TEXT patients were enrolled a median of 1.8 months post-surgery. SOFT patients were enrolled after adjuvant chemotherapy, after demonstration of premenopausal estradiol level, at a median of 9.8 months post-surgery. To avoid guarantee-time bias, the observation periods for analysis were re-aligned forwards, by defining a landmark time point at 1 year after the final dose of chemotherapy, which ensured that all SOFT patients could have reached the first 3-month protocol visit (supplementary Figure S1, available at *Annals of Oncology* online). Among TEXT and SOFT patients, the landmark was a median of 15.5 months [interquartile range (IQR) 14.3–16.0 months] and 8.1 months (IQR 6.3–9.8 months) post-enrollment.

The primary endpoint was breast cancer-free interval (BCFI), defined as the time interval beginning 1 year after final dose of adjuvant chemotherapy until the first appearance of invasive local-regional or distant recurrence or invasive contralateral breast cancer; in the absence of an event, BCFI was censored at date of last visit (or date of death without breast cancer event). The secondary endpoint was distant recurrence-free interval (DRFI), similarly defined beginning 1 year after final dose of adjuvant chemotherapy until the first appearance of invasive distant recurrence. BCFI was the chosen endpoint, rather than DFS, to disregard second (non-breast) invasive malignancies that occurred at similar frequencies across treatment groups.

Because timing of triptorelin initiation with chemotherapy was not randomized and there were differences in patient characteristics and prognostic features between TEXT and SOFT patients, the analysis used an inverse probability of 'treatment' weighting (IPTW) analysis using a propensity score [20]. The propensity score for the probability of concurrent versus sequential triptorelin (i.e. TEXT versus SOFT enrollment), conditional on measured patient, disease and treatment covariates, used logistic regression (supplementary Table S1, available at *Annals of Oncology* online). The covariates were pre-specified as those believed to be prognostic and potentially associated with enrollment into the trials, without use of variable-selection procedures [20], as presented in Table 1. The primary analysis used age at diagnosis; as sensitivity analysis, the analysis was repeated using age at enrollment (supplementary data, available at *Annals of Oncology* online). We calculated average treatment effect in the 'treated' (ATT) weights referenced to the TEXT population with concurrent triptorelin and used absolute standardized differences in characteristics between groups as diagnostic tool [21] (supplementary Table S2, available at *Annals of Oncology* online). An IPTW log-rank test and IPTW Kaplan–Meier estimates of time-to-event were estimated [22], as well as hazard ratios (HR) with 95% confidence intervals from an IPTW Cox model using robust standard errors.

Results

The eligible population included 1320 HR+/HER2-negative premenopausal patients who initiated triptorelin concurrently with chemotherapy in TEXT (concurrent), and 654 premenopausal patients who initiated triptorelin after adjuvant chemotherapy in SOFT (sequential; Figure 1). The estimated 5-year BCFI was 88.6% (±1.0%) and 86.4% (±1.4%) among TEXT and SOFT patients, respectively, based on data from time of trial enrollment (i.e. before introducing landmark and IPTW analyses). After introducing the landmark analysis, the final analysis population included 1872 patients who remained alive, disease-free and in follow-up at the landmark of 1 year since the final dose of

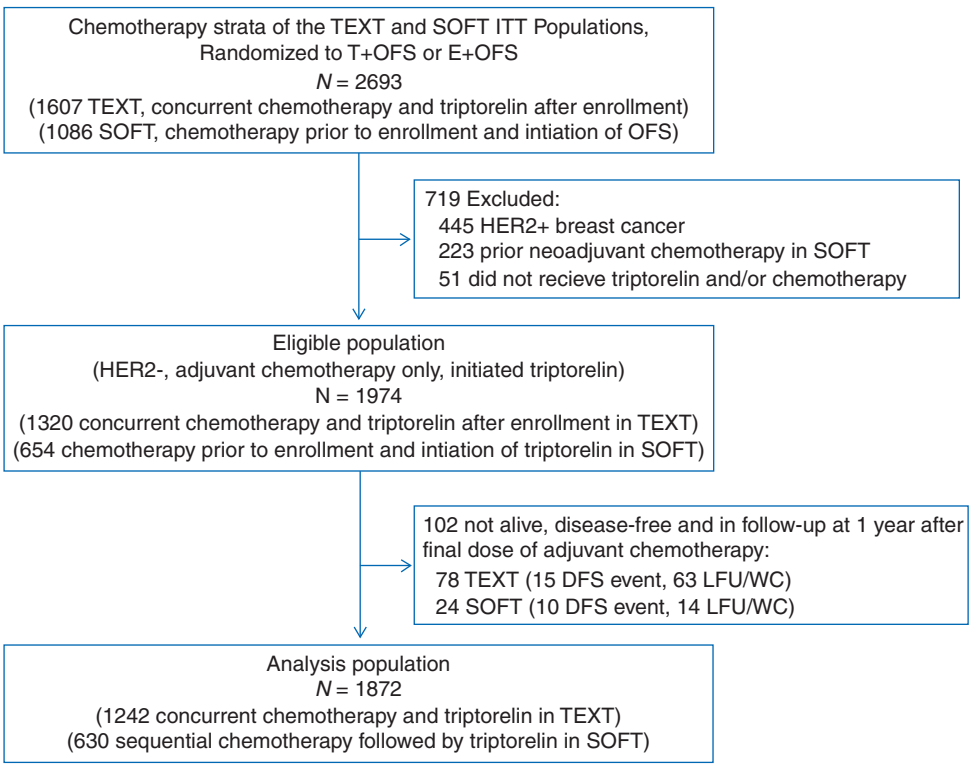

Figure 1. Flow diagram for defining the eligible population from TEXT and SOFT and the final analysis population.

Table 1. Patient, disease and treatment characteristics of the analysis population, according to timing of triptorelin (GnRH-agonist) initiation with chemotherapy (trial)

	Timing of triptorelin initiation and chemotherapy (trial)						Absolute standardized difference
	Concurrent (TEXT)		Sequential (SOFT)		All		
	N	%	*N*	%	*N*	%	
N patients	1242	100.0	630	100.0	1872	100.0	
Race/ethnicity							
Other/unknown	54	4.3	47	7.5	101	5.4	0.132
Black/African American	30	2.4	25	4.0	55	2.9	0.088
Hispanic/Latino/South American native	119	9.6	41	6.5	160	8.5	0.113
White/Caucasian	1039	83.7	517	82.1	1556	83.1	0.042
Age at diagnosis							
<35	140	11.3	140	22.2	280	15.0	0.296
35–39	220	17.7	192	30.5	412	22.0	0.302
40–44	435	35.0	197	31.3	632	33.8	0.080
45–49	383	30.8	83	13.2	466	24.9	0.436
50+	64	5.2	18	2.9	82	4.4	0.117
Year of diagnosis							
2003–2006	687	55.3	293	46.5	980	52.4	–
2007–2011	555	44.7	337	53.5	892	47.6	–
Age at enrollment							
<35	136	11.0	122	19.4	258	13.8	0.236
35–39	214	17.2	173	27.5	387	20.7	0.247
40–44	432	34.8	205	32.5	637	34.0	0.047
45–49	394	31.7	106	16.8	500	26.7	0.353
50+	66	5.3	24	3.8	90	4.8	0.072
Year of enrollment							
2003–2006	636	51.2	190	30.2	826	44.1	–
2007–2011	606	48.8	440	69.8	1046	55.9	–
BMI at enrollment							
Normal (<25)	671	54.0	275	43.7	946	50.5	0.209
Overweight (25 to < 30)	318	25.6	168	26.7	486	26.0	0.024
Obese (≥30)	235	18.9	175	27.8	410	21.9	0.211
Unknown	18	1.4	12	1.9	30	1.6	0.035
Menstruation status at enrollment							
Normal	1080	87.0	233	37.0	1313	70.1	1.201
Irregular	86	6.9	184	29.2	270	14.4	0.605
Persistent amenorrhea	56	4.5	201	31.9	257	13.7	0.759
Unknown	20	1.6	12	1.9	32	1.7	0.022
Performance status at enrollment							
Fully active (90–100)	1199	96.5	579	91.9	1778	95.0	0.200
Restricted/ambulatory(50–80)/unknown	43	3.5	51	8.1	94	5.0	0.200
Hormone receptor status							
ER+/PR+	1081	87.0	526	83.5	1607	85.8	0.100
Other	161	13.0	104	16.5	265	14.2	0.100
Tumor size (path)							
≤2 cm	566	45.6	332	52.7	898	48.0	0.143
>2 cm	657	52.9	287	45.6	944	50.4	0.147
Unknown	19	1.5	11	1.7	30	1.6	0.017
No. nodes positive							
pN0	385	31.0	280	44.4	665	35.5	0.280
pN + 1–3	548	44.1	241	38.3	789	42.1	0.119
pN + 4+	309	24.9	109	17.3	418	22.3	0.187
Tumor grade							
1	162	13.0	118	18.7	280	15.0	0.156
2	679	54.7	329	52.2	1008	53.8	0.049
3	401	32.3	183	29.0	584	31.2	0.070

Continued

Table 1. *Continued*

	Timing of triptorelin initiation and chemotherapy (trial)						Absolute
	Concurrent (TEXT)		Sequential (SOFT)		All		standardized difference
	N	%	*N*	%	*N*	%	
Lymphovascular invasion							
No/unknown	648	52.2	396	62.9	1044	55.8	0.217
Yes	594	47.8	234	37.1	828	44.2	0.217
Local therapy							
Mastectomy, no RT	309	24.9	139	22.1	448	23.9	0.066
Mastectomy with RT	304	24.5	186	29.5	490	26.2	0.114
BCS with RT	623	50.2	303	48.1	926	49.5	0.041
Other	6	0.5	2	0.3	8	0.4	0.026
Chemotherapy regimen							
Anthracycline-based	702	56.5	306	48.6	1008	53.8	0.160
Taxane-based	63	5.1	46	7.3	109	5.8	0.093
Anthracycline+taxane-based	448	36.1	273	43.3	721	38.5	0.149
Other/unknown	29	2.3	5	0.8	34	1.8	0.124
Chemotherapy duration							
≤12 weeks	497	40.0	190	30.2	687	36.7	0.208
>12 to < 24 weeks	588	47.3	323	51.3	911	48.7	0.079
≥24 weeks	157	12.6	117	18.6	274	14.6	0.164
Chemotherapy included cyclophosphamide							
Tamoxifen before enrollment	1229	99.0	618	98.1	1847	98.7	–
No	1242	100	346	54.9	–	–	–
Yes[a]	0	0	284	45.1	–	–	
Endocrine therapy assignment							
Tamoxifen+OFS	630	50.7	319	50.6	949	50.7	–
Exemestane+OFS	612	49.3	311	49.4	923	49.3	–

Absolute standardized difference is the absolute value of the difference in sample proportions of the two groups divided by the pooled standard deviation.

[a]Prior endocrine therapy was allowed in SOFT but not TEXT. Among the 284 patients, the median duration of prior tamoxifen was 17 weeks (interquartile range, 10–23 weeks).

BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; BCS, breast-conserving surgery; RT, radiotherapy; OFS, ovarian function suppression.

adjuvant chemotherapy, 1242 and 630 who received concurrent and sequential triptorelin, respectively.

Differences between the two groups were evident in most characteristics. In particular, SOFT patients receiving sequential triptorelin were younger than TEXT patients receiving concurrent triptorelin (median age at diagnosis 39 and 43 years, respectively). The median duration of adjuvant chemotherapy was 18 weeks (IQR 12–18 weeks) in both groups. At the landmark time point, 85% of concurrent and 87% of sequential patients continued triptorelin, 11% and 8% had undergone ovarian ablation, respectively, and 5% had ceased OFS early. In total 93% of patients continued the assigned oral endocrine therapy (91% and 95%, respectively).

There were 231 (12%) breast cancer events in the 2 groups at post-landmark median follow-up of 4.7 and 4.9 years. The concurrent use of triptorelin with chemotherapy was not associated with a significant difference in BCFI (HR = 1.11, 95% CI 0.72–1.72; $p = 0.72$), with an estimated 89.1% (±1.0%) and 89.0% (±2.9%) patients breast cancer-free at 4 years post-landmark, with concurrent and sequential triptorelin initiation, respectively (Figure 2). The results were similar for DRFI; 187 distant recurrences were reported, with estimated 90.8% (±0.9%) and 90.5% (±2.7%) patients distant recurrence-free in the concurrent and sequential groups, respectively, at 4 years post-landmark (HR = 0.96, 95% CI 0.60–1.53; $p = 0.86$).

There was no evidence of differential effectiveness of concurrent triptorelin among younger women (<40 years at diagnosis; $n = 692$) than older premenopausal women at this point in follow-up (Figure 3). The estimated BCFI at 4 years post-landmark with concurrent and sequential triptorelin, respectively, was 84.8% (±2.0%) and 82.9% (±3.5%) for women aged <40 years at diagnosis (HR = 1.13, 95% CI 0.69–1.84), and 90.8% (±1.1%) and 91.7% (±3.4%) for those ≥40 years at diagnosis (HR = 1.10, 95% CI 0.57–2.14).

Discussion

TEXT and SOFT demonstrated the benefit of adding OFS to tamoxifen alone in high-risk patients remaining premenopausal after

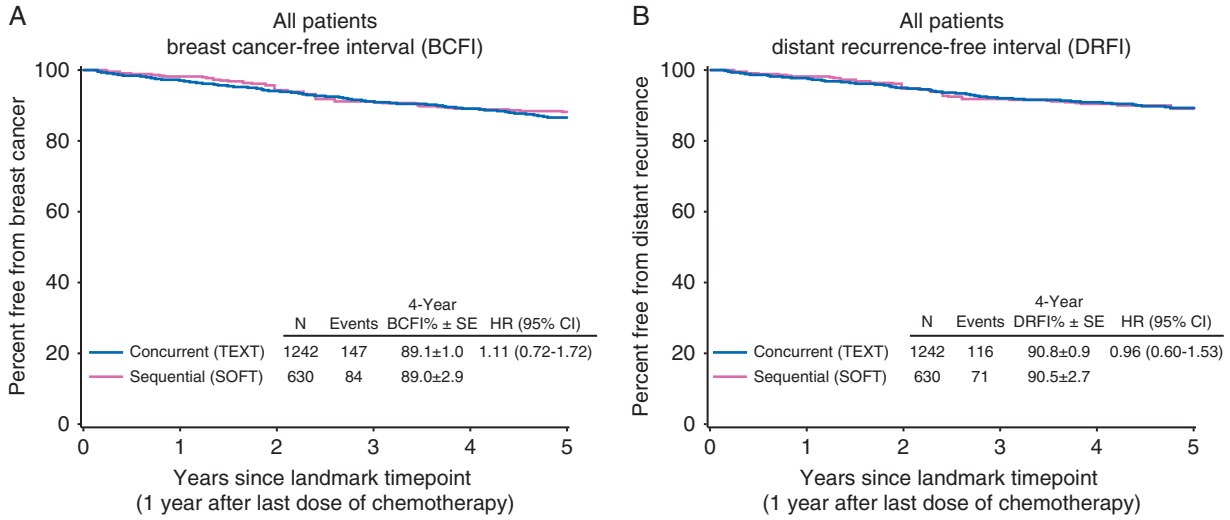

Figure 2. Breast cancer-free interval (BCFI; A) and distant recurrence-free interval (DRFI; B) according to timing of triptorelin initiation with chemotherapy, from the landmark time point beginning 1 year after the final dose of adjuvant chemotherapy.

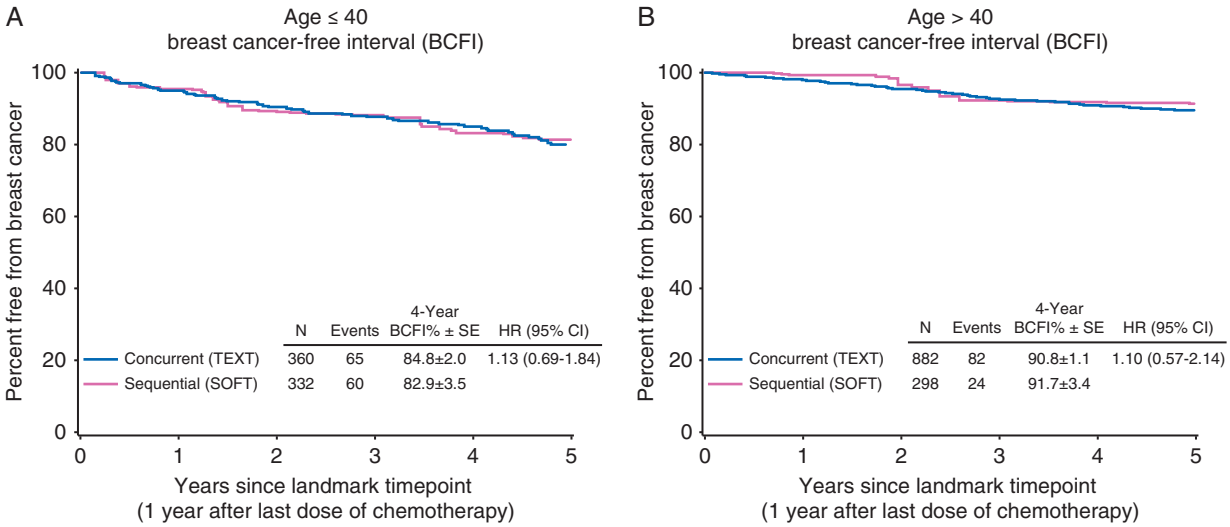

Figure 3. Breast cancer-free interval (BCFI) for women aged <40 years (A) and ≥40 years (B) at diagnosis, according to timing of triptorelin initiation with chemotherapy, from the landmark time point beginning 1 year after the final dose of adjuvant chemotherapy.

adjuvant chemotherapy and of exemestane over tamoxifen when combined with OFS. When chemotherapy was also given, OFS initiation differed between TEXT and SOFT (concurrently or sequentially with chemotherapy, respectively) to accommodate different attitudes worldwide. The trials were not designed to elucidate an optimal strategy. The sequential administration, by postponing an effective targeted therapy in premenopausal patients at higher-risk of relapse, might reduce treatment efficacy. On the other hand, the concurrent strategy might interfere with the cytotoxic activity of chemotherapy and will mask and abrogate the therapeutic role of CIA, especially in older premenopausal women, resulting in 5 years of potentially unnecessary and costly GnRH-agonist therapy. To investigate this relevant clinical issue, we analyzed 1872 patients with HER2-negative breast cancer who received adjuvant triptorelin in SOFT/TEXT. Our analysis showed no difference in the BCFI between the concurrent and sequential triptorelin treatment groups, neither overall nor in the subgroup of women <40 years at diagnosis who are less likely to develop CIA, after about 5-years median follow-up.

Timing and sequencing of endocrine therapy and chemotherapy has not been adequately studied in early breast cancer [23]. The biologic evidence relates to tamoxifen, which works by a different endocrine mechanism than OFS [7, 24]. The tamoxifen-induced blockade in the G1-S phase of the cell cycle has been hypothesized to antagonize the antitumor effect of chemotherapy. The 2011 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview of adjuvant tamoxifen showed significant recurrence risk (RR) reduction regardless of its concurrent (RR = 0.62) or sequential (RR = 0.71) administration with chemotherapy [25]. A small number of neoadjuvant studies compared sequential chemotherapy followed by OFS to concurrent therapy. The NSABP B-52 trial, in which 46% of patients were premenopausal, recently showed that adding endocrine therapy (GnRH-agonist + AI) to neoadjuvant immunochemotherapy in

HR+/HER2-positive breast cancer was not antagonistic and did not increase toxicity [26]. The only large trials studying OFS concurrently with chemotherapy assessed ovarian/fertility preservation, but the majority were restricted to HR-negative breast cancer [27]. Reassuringly, the breast cancer outcomes have not been compromised by the addition of concomitant GnRH-agonist [27].

Our analysis has limitations, mainly its non-randomized nature and the planned difference in enrollment timing in SOFT and TEXT, which led to inherent differences in the populations. Despite the use of IPTW and landmark analysis to balance the characteristics between concurrent and sequential OFS groups and align the periods of observation as in a randomized trial, the methodology may not have adequately overcome these issues. Moreover, median follow-up for SOFT/TEXT was <6 years, and differences in concurrent versus sequential OFS and chemotherapy could appear only later in follow-up. Statistical power was limited, especially for the subgroup <40 years, and real differences between the strategies may not have been detected.

From a clinical perspective, as no randomized trial will be conducted to properly answer this question, when chemotherapy will also be given, clinicians and patients need to select the concurrent or sequential strategy of OFS on an individual basis. Which considerations may help in guiding this decision? Concurrent administration does not increase chemotherapy-related adverse events [15] and the possibility to avoid permanent menopause and its consequences is attractive for younger premenopausal women. The rate of CIA is age- and regimen-dependent: most very young women (<35 years) resume menses after chemotherapy and could consider concurrent OFS thus receiving and completing a therapy that has proved to be particularly effective in this age group [14] 6 months earlier. In premenopausal women, the possibility to preserve fertility in addition to the adjuvant effect is especially attractive for those not having completed family planning. In contrast, in women already approaching menopause, delaying GnRH-agonist administration until resumption of menses after chemotherapy may avoid unnecessary and costly drug administration. For women on tamoxifen following chemotherapy, the evaluation of ovarian function can be challenging, especially in patients developing amenorrhea [28]. SOFT/TEXT data represent the only evidence available in premenopausal patients from a large sample within controlled clinical trials: they support clinicians and patients selecting the concurrent or sequential strategy of chemotherapy and OFS on an individual patient basis.

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