Age-Specific Nonpersistence of Endocrine Therapy in Postmenopausal Patients Diagnosed with Hormone Receptor–Positive Breast Cancer: A TEAM Study Analysis

WILLEMEN VAN DE WATER,^{a,b} ESTHER BASTIAANNET,^{a,b} ELYSÉE T.M. HILLE,^a
ELMA M. MEERSHOEK-KLEIN KRANENBARG,^a HEIN PUTTER,^c CAROLINE M. SEYNAEVE,^d
ROBERT PARIDAENS,^e ANTON J.M. DE CRAEN,^b RUDI G.J. WESTENDORP,^b GERRIT-JAN LIEFERS,^a
CORNELIS J.H. VAN DE VELDE^a

^aDepartment of Surgery, ^bDepartment of Gerontology and Geriatrics, and ^cDepartment of Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands; ^dDepartment of Medical Oncology, Erasmus University Medical Center-Daniel den Hoed, Rotterdam, The Netherlands; ^eDepartment of Internal Medicine, University Hospital Leuven, Leuven, Belgium

Key Words. Breast cancer • Elderly • Endocrine therapy • Persistence

Disclosures: Willemien van de Water: None; Esther Bastiaannet: None; Elysée T.M. Hille: None; Elma M. Meershoek-Klein Kranenbarg: None; Hein Putter: None; Caroline M. Seynaeve: Pfizer (support for travel expenses), Sanofi-Aventis (C/A); Robert Paridaens: Received investigator fees paid to the hospital for participation in the trial; Anton J.M. de Craen: None; Rudi G.J. Westendorp: None; Gerrit-Jan Liefers: None; Cornelis J.H. van de Velde: None.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

ABSTRACT

Background. Early discontinuation of adjuvant endocrine therapy may affect the outcome of treatment in breast cancer patients. The aim of this study was to assess age-specific persistence and age-specific survival outcome based on persistence status.

Methods. Patients enrolled in the Tamoxifen Exemestane Adjuvant Multinational trial were included. Nonpersistence was defined as discontinuing the assigned endocrine treatment within 1 year of follow-up because of adverse events, intercurrent illness, patient refusal, or other reasons. Endpoints were the breast cancer–specific and overall survival times. Analyses were stratified by age at diagnosis (<65 years, 65–74 years, ≥75 years).

Results. Overall, 3,142 postmenopausal breast cancer patients were included: 1,682 were aged <65 years, 951

were aged 65–74 years, and 509 were aged ≥75 years. Older age was associated with a higher proportion of nonpersistence within 1 year of follow-up. In patients aged <65 years, nonpersistent patients had lower breast cancer–specific and overall survival probabilities. In patients aged 65–74 years and patients aged ≥75 years, the survival times of persistent and nonpersistent patients were similar.

Conclusion. Nonpersistence within 1 year of follow-up was associated with lower breast cancer–specific and overall survival probabilities in patients aged <65 years, but it was not associated with survival outcomes in patients aged 65–74 years or in patients aged ≥75 years. These results suggest that extrapolation of outcomes from a young to an elderly breast cancer population may be insufficient and urge age-specific breast cancer studies. *The Oncologist* 2012;17:55–63

Correspondence: Cornelis J.H. van de Velde, M.D., Ph.D., Leiden University Medical Center, Albinusdreef 2, PO Box 9600, 2300 RC Leiden, The Netherlands. Telephone: 0031715262309; Fax: 0031715266750; e-mail: c.j.h.van_de_velde@lumc.nl. Received February 8, 2011; accepted for publication September 21, 2011; first published online in *The Oncologist Express* on December 30, 2011. ©Al-paMed Press 1083-7159/2011/\$40.00/0 <http://dx.doi.org/10.1634/theoncologist.2011-0037>

INTRODUCTION

In the developed world, breast cancer is the most frequently diagnosed malignancy in females [1]. The role of adjuvant endocrine therapy in middle-aged hormone receptor–positive breast cancer patients is well established—5 years of endocrine treatment with tamoxifen results in an 11.8% lower absolute recurrence rate and 9.2% lower breast cancer mortality rate after 15 years of follow-up [2].

Observational and nonobservational studies, however, show a substantial proportion of nonpersistence or discontinuation during 5 years of endocrine therapy. A recent meta-analysis evaluated persistence with tamoxifen or an aromatase inhibitor in clinical trials and reported that, overall, 23%–28% of patients followed for ≥ 4 years discontinued endocrine therapy earlier than recommended [3]. Observational studies show a comparable or even higher nonpersistence percentage [4–7]—up to 49% nonpersistence rate after 5 years of follow-up [7].

In a recent review, Ruddy and Partridge [8] stated that nonpersistence was associated with greater consumption of health care resources, including more physician visits, higher hospitalization rates, and longer hospital stays [8]. Moreover, nonpersistence may impede the efficacy of endocrine therapy. To date, however, few data have been published on the effects of nonpersistence in oncology [8].

Evidence is particularly scarce in the elderly breast cancer population. Despite comprising a large proportion of breast cancer patients, elderly breast cancer patients remain underrepresented in clinical trials [9]—an estimated 1%–2% of elderly patients participate in clinical trials [10]. Unlike many breast cancer trials, the Tamoxifen, Exemestane, Adjuvant, Multinational (TEAM) trial [11] had no upper age limitation, thereby providing a unique opportunity to focus on elderly breast cancer patients. The aim of this study was to assess age-specific nonpersistence within 1 year of follow-up. Moreover, we evaluated age-specific outcome by nonpersistence status at 1 year of follow-up.

METHODS

TEAM Trial Design

The TEAM trial was a randomized, adjuvant, phase III, multinational, open-label study conducted in postmenopausal women with estrogen- and/or progesterone receptor–positive tumors. Patients were randomized to receive either exemestane (25 mg once daily) for 5 years or tamoxifen (20 mg once daily) for 2.5–3 years followed by exemestane (25 mg once daily) for 2–2.5 years, for a total of 5 years. Participants were enrolled in Belgium, The Netherlands, the U.K., Ireland, the U.S., Japan, Greece, Germany, and France ($n = 9,766$) [11]. Extensive eligibility criteria were published in earlier reports [11, 12]. In short, postmenopausal patients with histologically confirmed breast adenocarcinoma who completed local therapy with curative intent, that is, without evidence of metastatic disease, were eligible.

Current Study Design

Figure 1 shows the flow chart of the current study. Inclusion was restricted to patients from The Netherlands ($n = 2,753$)

Figure 1. Study flow chart.

Abbreviations: BE, Belgium; NL, The Netherlands; TEAM, Tamoxifen Exemestane Adjuvant Multinational.

and Belgium ($n = 414$) because of available data on comorbidity. Patients who never started study medication and patients with missing data regarding duration of randomized therapy were excluded from analyses ($n = 25$), which resulted in a study population of 3,142 subjects.

Persistence

Patients were categorized as persistent or nonpersistent depending on whether or not they continued the allocated treatment for ≥ 1 year. Nonpersistence was defined as discontinuation of the allocated endocrine therapy within 1 year of follow-up because of adverse events, intercurrent illness, patient refusal not otherwise specified, or other reasons. Persistent patients continued the allocated endocrine therapy for ≥ 1 year. Patients who died or developed a relapse within 1 year of follow-up while on study medication were considered to be persistent. Persistence status was evaluated at each follow-up visit. Patients were assessed every 3 months during the

first year of follow-up and at least once yearly thereafter. At follow-up visits, patients were asked whether or not they (dis)continued randomized therapy. In cases of nonpersistence, the date and reason for nonpersistence were recorded by the treating physician. By calculating persistence in the first year, persistence could be used as a fixed covariate in survival analyses following the first year of follow-up (landmark method) [13]. Alternative endocrine therapy in cases of nonpersistence was defined as none, crossover, or other therapy.

Patients were categorized into three age groups (<65 years, 65–74 years, and ≥75 years) according to recommendations at the Annual Meeting of the International Society of Geriatric Oncology in 2009. Endpoints were the breast cancer–specific survival duration and overall survival duration. The breast cancer–specific survival duration was defined as the time from randomization to death resulting from breast cancer, whereas the overall survival time was defined as the time from randomization to death from any cause.

Statistical Analysis

Statistical analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL) and R statistical package (R Development Core Team, Wenen, Austria). To compare proportional differences among age categories, the Pearson χ^2 test was used. Binary logistic regression analysis was used to assess predictive factors for nonpersistence within 1 year. Kaplan–Meier curves were plotted and a Cox proportional hazards model was used to assess survival differences with respect to persistence status at 1 year of follow-up. Persistence was treated according to the landmark method, using 1 year of follow-up as a landmark [13]. Patients who reached an endpoint within the first year of follow-up and patients on study medication who had <1 year of follow-up could not be taken into account and were excluded from survival analyses ($n = 93$) (Fig. 1). In line with others who investigated breast cancer outcome by adherence by means of a landmark analysis [14], a cutoff of 1 year was chosen because of a considerable proportion of nonpersistence but occurrence of few events within 1 year of follow-up. Moreover, we aimed to exclude bias resulting from nonpersistence because of switch issues in the sequential arm. Covariates were included in the multivariate model if they were of clinical significance; multivariate analyses included the histological Bloom–Richardson grade (1–3); estrogen receptor status (positive or negative); progesterone receptor status (positive or negative); tumor (T) stage (T1–T4); node (N) status (negative or positive); presence of cardiac, central nervous system, endocrine, gastrointestinal, genitourinary, or musculoskeletal comorbidities (all, no, or yes); most extensive surgery (wide local excision or mastectomy); axillary surgery (yes or no); radiotherapy (yes or no); adjuvant chemotherapy (yes or no); and endocrine therapy (tamoxifen followed by exemestane or exemestane alone). Because of collinearity, the influence of alternative treatment could be assessed in nonpersistent patients only. To assess whether or not the association between nonpersistence within 1 year of follow-up and survival outcome was different among age categories, we tested for interaction between age and persistence status at 1 year of follow-up. To

assess the sensitivity of the landmark, alternative cutoff points were analyzed (0.5 years and 1.5 years). All statistical tests were two-sided. A p -value <.05 was considered to be statistically significant.

RESULTS

Overall, 3,142 patients were included, of whom 1,682 were aged <65 years (54%; median age, 58.4 years), 951 were aged 65–74 years (30%; median age, 69.7 years), and 509 were aged ≥75 years (16%; median age, 79.3 years). The median follow-up times from randomization were 5.0 years, 5.0 years, and 4.8 years, respectively. Baseline characteristics by age at diagnosis are shown in Table 1. Older age was associated with a different histological grade ($p = .004$) and larger tumor ($p < .001$); the nodal status, however, was similar among age categories. The presence of one or more cardiac, central nervous system, endocrine, gastrointestinal, genitourinary, and musculoskeletal comorbidity increased with older age (all p -values <.001). In addition, the proportion of patients treated with mastectomy was significantly greater with older age, whereas administration of radiotherapy and chemotherapy was significantly lower (all p -values <.001).

Overall, 256 patients (8.1%) discontinued the allocated endocrine therapy within 1 year of follow-up—116 (7.4%) in the exemestane arm and 140 (8.9%) in the sequential arm ($p = .118$). Nonpersistence within 1 year of follow-up was more common in the older age groups (<65 years, 7.0%; 65–74 years, 7.5%; ≥75 years, 13.2%; $p < .001$). As shown in Table 2, reasons for nonpersistence within 1 year of follow-up did not differ among the age categories ($p = .561$). In all age categories, the presence of adverse events was the most frequently reported reason for nonpersistence (85%, 83%, and 89%, respectively).

To gain insight into underlying mechanisms, we assessed predictive factors for nonpersistence within 1 year of follow-up in all age categories (supplemental online Table 1A, 1B, 1C). In patients aged <65 years, the presence of central nervous system, gastrointestinal, and genitourinary comorbidities, a mastectomy as the most extensive surgery, and the omission of radiotherapy were associated with nonpersistence within 1 year of follow-up. Multivariate analyses showed that gastrointestinal comorbidity and omission of radiotherapy were independent predictive factors for nonpersistence within 1 year of follow-up. In patients aged 65–74 years, no predictive factors for nonpersistence could be identified. In patients aged ≥75 years, larger tumor size, wide local excision as the most extensive surgical treatment, and omission of radiotherapy were independent predictive factors for nonpersistence within 1 year of follow-up. In cases of nonpersistence within 1 year of follow-up, older age was associated with less frequent administration of alternative endocrine treatment (78.8%, 80.3%, and 61.2%, respectively; $p = .013$) (data not shown).

At database lock, the numbers of deaths were 173 (10.3%) in patients aged <65 years, 133 (14.0%) in patients aged 65–74 years, and 154 (30.3%) in patients aged ≥75 years. The numbers of deaths resulting from breast cancer were 146 (8.7%), 88 (9.3%), and 60 (11.8%), respectively. Figure 2 de-

Table 1. Baseline characteristics by age category

Characteristic	Age <65 yrs (n = 1,682)		Age 65–74 yrs (n = 951)		Age ≥75 yrs (n = 509)		p-value
	n	%	n	%	n	%	
Histological grade (BR)							.004
Well	240	14.3	142	14.9	70	13.8	
Intermediate	707	42.0	415	43.6	235	46.2	
Poor	647	38.5	339	35.6	157	30.8	
Unknown	88	5.2	55	5.8	47	9.2	
Estrogen receptor							.002
Positive	1,629	96.8	942	99.1	503	98.8	
Negative	52	3.1	9	0.9	6	1.2	
Not performed	1	0.1	0	0.0	0	0.0	
Progesterone receptor							.416
Positive	1,244	74.0	698	73.4	387	76.0	
Negative	347	20.6	209	22.0	104	20.4	
Not performed	91	5.4	44	4.6	18	3.5	
T stage							<.001
0, is	2	0.1	0	0.0	0	0.0	
1	802	47.7	443	46.2	128	25.1	
2	762	45.3	442	46.5	332	65.2	
3, 4	111	6.6	66	6.9	49	9.6	
Unknown	5	0.3	0	0.0	0	0.0	
Nodal status							.090
Negative	486	28.9	299	31.4	168	33.0	
Positive	1,194	71.0	652	68.6	339	66.6	
Unknown	2	0.1	0	0.0	4	0.1	
Presence of comorbidity							
Cardiac	514	30.6	442	46.5	280	55.0	<.001
CNS	151	9.0	104	10.9	79	15.5	<.001
Endocrine	249	14.8	195	20.5	117	23.0	<.001
Gastrointestinal	356	21.2	272	28.6	151	29.7	<.001
Genitourinary	466	27.7	220	23.1	145	28.5	.020
Musculoskeletal	382	22.7	276	29.0	193	37.9	<.001
Most extensive surgery							<.001
WLE	863	51.3	424	44.6	129	25.3	
Mastectomy	818	48.7	527	55.4	380	74.7	
Axillary surgery							.285
Yes	1,341	79.7	740	77.8	413	81.1	
No	341	20.3	211	22.2	96	18.9	
Radiotherapy							<.001
Yes	1,201	71.4	597	62.8	243	47.7	
No	478	28.4	353	37.1	266	52.3	
Unknown	3	0.2	1	0.1	0	0.0	
Chemotherapy							<.001
Yes	936	55.6	103	10.8	1	0.2	
No	746	44.4	847	89.1	508	99.8	
Unknown	0	0.0	1	0.1	0	0.0	
Randomization							.880
Tam → Exe	837	49.8	483	50.8	255	50.1	
Exemestane	845	51.2	468	49.2	254	49.9	

p-values set in bold font are statistically significant.

Abbreviations: BR, Bloom–Richardson; CNS, central nervous system; Tam → Exe, tamoxifen followed by exemestane; WLE, wide local excision.

Table 2. Reason for nonpersistence within 1 year of follow-up by age category

Reason for nonpersistence	Age <65 yrs (n = 118)		Age 65–74 yrs (n = 71)		Age ≥75 yrs (n = 67)		p-value
	n	%	n	%	n	%	
							.561
Adverse events	100	84.7	59	83.1	60	89.6	
Intercurrent illness	4	3.4	4	5.6	2	3.0	
Patient refusal, not otherwise specified	10	8.5	3	4.2	2	3.0	
Other reason	4	3.4	5	7.0	3	4.5	

picts the cumulative incidence of deaths resulting from breast cancer and deaths resulting from other causes from the landmark by persistence status at 1 year of follow-up, stratified by age at diagnosis. As shown in Table 3, patients aged <65 years who were nonpersistent within 1 year of follow-up had a lower breast cancer–specific survival probability (multivariate hazard ratio [HR], 2.76; 95% confidence interval [CI], 1.55–4.90; $p = .001$). For the overall survival probability, comparable results were observed (multivariate HR, 2.83; 95% CI, 1.65–4.85; $p < .001$) (Table 3). In contrast, nonpersistence within 1 year of follow-up was not associated with either the breast cancer–specific survival duration or the overall survival time in patients aged 65–74 years (multivariate $p = .387$ and $.659$, respectively) or in patients aged ≥75 years (multivariate $p = .982$ and $.942$, respectively).

Additional survival analyses including an interaction term between persistence status at 1 year of follow-up and age confirmed a significant interaction for the breast cancer–specific survival time ($p = .031$) but not for the overall survival time ($p = .140$). To assess the sensitivity of the landmark, we performed additional survival analyses using alternative landmark cutoffs (0.5 years and 1.5 years), which did not alter the results (data not shown). To account for a potential lack of power in patients aged ≥75 years, we performed additional survival analyses in which patients aged 65–74 years and patients aged ≥75 years were combined. Again, nonpersistence within 1 year of follow-up was not associated with the breast cancer–specific survival probability (univariate HR, 0.93; 95% CI, 0.49–1.77; $p = .819$; multivariate HR, 0.81; 95% CI, 0.39–1.69; $p = .675$). For the overall survival outcome, we observed comparable results (univariate HR, 1.29; 95% CI, 0.87–1.93; $p = .206$; multivariate HR, 1.19; 95% CI, 0.76–1.87; $p = 0.440$). Additional analyses were performed to evaluate the influence of alternative treatment in cases of nonpersistence (data not shown). In patients who were nonpersistent, alternative treatment was not associated with the breast cancer–specific or overall survival outcome in any age category (multivariate analyses for breast cancer–specific survival outcome: $p = 0.401$, $.576$, and $.426$, respectively; multivariate analyses for overall survival outcome: $p = .314$, $.325$, and $.328$, respectively).

DISCUSSION

Summary

In this study, older age was associated with a higher proportion of nonpersistence within 1 year of follow-up. Patients aged <65 years who were nonpersistent within 1 year of follow-up had markedly worse breast cancer–specific and overall survival outcomes. However, no differences were observed for patients aged 65–74 years or for patients aged ≥75 years.

Imbedding in Literature

Nonpersistence has been evaluated in other endocrine therapy trials. The Intergroup Exemestane Trial randomized patients to receive 2–3 years of tamoxifen or 2–3 years of exemestane after 2–3 years of tamoxifen. Treatment was stopped early in 14% of the study population. Because randomization took place after 2–3 years of tamoxifen, early nonpersistence was not taken into account [15]. Of all patients included in the Arimidex and Tamoxifen Alone or in Combination trial, 76% of patients on anastrozole and 72% of tamoxifen-treated patients were persistent nearly 47 months after diagnosis [16]. Fisher et al. [17] evaluated the efficacy of 5 years versus >5 years of tamoxifen in node-negative breast cancer patients. During the first 5 years after randomization, 23% of patients discontinued the assigned therapy. Five years of tamoxifen in a preventive setting showed a nonpersistence proportion of 24%–36% [18, 19].

Several observational studies have reported on age-specific persistence. Fink et al. [4] did not observe a relation between age and discontinuation within 2 years of follow-up in a cohort of 516 breast cancer patients on tamoxifen. Similar results were found in a cohort study by Demissie et al. [6]. Hershman et al. [20] studied persistence and adherence in a historical cohort of 8,769 patients who received either tamoxifen or an aromatase inhibitor. Persistence and adherence were evaluated by automated pharmacy records. Patients aged <40 years and patients aged ≥75 years were most likely to discontinue endocrine therapy within 4.5 years of follow-up. Partridge et al. [21] studied tamoxifen adherence in a cohort of 2,378 breast cancer patients. Adherence was defined as the number of days covered by a filled prescription in the first year of therapy. A lower adherence rate was observed in both women aged <45 years

Figure 2. Cumulative incidence of death resulting from breast cancer and from other causes by persistence status at 1 year follow-up, by age at diagnosis.

and women aged ≥ 85 years. These results are consistent with a cohort study by Barron et al. [5] among 2,816 breast cancer patients aged ≥ 35 years on tamoxifen. Patients aged 35–44 years and patients aged ≥ 75 years were most likely to discontinue tamoxifen within 1 year of follow-up. In addition, a recent study among 961 breast cancer patients by Owusu et al. [7] showed that age ≥ 75 years was an independent predictor of tamoxifen discontinuation before completion of 5 years of therapy.

In most observational studies, higher age is associated with lower persistence [5, 7, 20, 21]. Differences in proportions may have been affected by the use of either adherence or persistence as the primary endpoint. Persistence is de-

fined as the duration of time over which a patient continues to fill prescriptions [22]. A related endpoint is adherence, which is defined as whether medication is taken as consistently as prescribed. This can be calculated by dividing the quantity of pills dispensed by the total days covered by the prescription [21, 23]. In contrast to other studies, we assessed persistence in the first year of follow-up in order to study survival outcomes by persistence status. In addition, inclusion in the current study was restricted to postmenopausal patients. Moreover, one has to take into account that the setting of a clinical trial generally results in higher persistence rates [22], possibly as a result of patient selection and attention [23–25].

Table 3. Breast cancer–specific and overall survival outcomes by age category and persistence status

Persistence status by age category	4-yr survival	Univariate		Multivariate ^a	
		HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Breast cancer–specific survival					
Age <65 years			.001		.001
Persistent ≥1 yr	94%	1 (reference)		1 (reference)	
Persistent <1 yr	82%	2.55 (1.51–4.33)		2.76 (1.55–4.90)	
Age 65–74 yrs			.356		.387
Persistent ≥1 yr	92%	1 (reference)		1 (reference)	
Persistent <1 yr	94%	0.58 (0.18–1.84)		0.59 (0.18–1.94)	
Age ≥75 yrs			.731		.982
Persistent ≥1 yr	90%	1 (reference)		1 (reference)	
Persistent <1 yr	90%	1.15 (0.52–2.56)		0.99 (0.37–2.62)	
Overall survival					
Age <65 yrs			<.001		<.001
Persistent ≥1 yr	93%	1 (reference)		1 (reference)	
Persistent <1 yr	80%	2.49 (1.51–4.09)		2.83 (1.65–4.85)	
Age 65–74 yrs			.930		.659
Persistent ≥1 yr	89%	1 (reference)		1 (reference)	
Persistent <1 yr	86%	1.03 (0.50–2.12)		1.18 (0.57–2.47)	
Age ≥75 yrs			.524		.942
Persistent ≥1 yr	76%	1 (reference)		1 (reference)	
Persistent <1 yr	76%	1.17 (0.72–1.90)		0.98 (0.54–1.76)	

p-values set in bold font are statistically significant.

^aMultivariate analyses were adjusted for histological grade, estrogen status, progesterone status, T stage, N status, cardiac/central nervous system/endocrine/gastrointestinal/genitourinary and musculoskeletal comorbidities, most extensive surgery, axillary surgery, radiotherapy, adjuvant chemotherapy, and endocrine therapy. Abbreviations: CI, confidence interval; HR, hazard ratio.

Exclusion of Survival Bias

Because patients were not randomized by persistence status, we acknowledge the limitations of discussing survival by persistence status at 1 year of follow-up. Patients with a worse prognosis or higher intrinsic mortality may have had a higher tendency to become nonpersistent and thereby bias the survival analyses. In patients aged <65 years, nonpersistent patients more often had central nervous system, gastrointestinal, and genitourinary comorbidities. However, in patients aged ≥75 years, who have more comorbid diseases (Table 1), no differences between persistent and nonpersistent patients were observed (supplemental online Table 1). Moreover, no association between persistence status and overall survival duration was demonstrated (Table 3). Therefore, it is unlikely that the presence of comorbid disease had a major impact on the association between persistence and survival outcomes in the eldest patients. In addition, administration of alternative endocrine therapy in cases of nonpersistence may have biased the survival analyses. However, additional analyses did not indicate a survival benefit for nonpersistent patients who received alternative therapy. A lack of power was not likely to have

had a major influence on our findings—analyses in which patients aged 64–75 years and patients aged ≥75 years were combined showed similar results.

Explanation of Results

It is tempting to speculate on the underlying mechanisms that could explain the results presented in this study. Both patients and physicians might be more likely to discontinue treatment with older patient age. It has been suggested that persistence in the elderly may be impaired by psychosocial issues such as less social support and higher incidences of cognitive and functional impairment [26]. Sharkness and Snow showed that elderly patients with more than one chronic illness requiring the use of multiple drugs were more likely to be adherent [27]. Comparable associations have been observed for different numbers of prescriptions [4, 28]. On the other hand, others have observed lower adherence rates in patients using multiple drugs [29–31].

Although little is known about the implications of nonpersistence, it is well known that the duration of adjuvant endocrine therapy is strongly associated with survival outcomes in young and middle-aged breast cancer patients [2]. However,

evidence in the elderly is lacking. The elderly might respond differently to a certain therapy. The presence of comorbidities may affect anticancer therapy [32]. Polypharmacy may cause drug interactions [33] and may alter the pharmacokinetics of anticancer therapy [32]. These findings hint at potential age-specific therapy dynamics, but this should be investigated in further studies. Moreover, because of a higher risk for competing mortality, the proportion of deaths attributable to breast cancer decreases with age. A higher competing risk for death with increasing age may play a role in assessing survival differences in elderly breast cancer patients.

Strengths and Limitations

The major strength of this study is the ability to study a large group of incident breast cancer patients. Trial data comprise highly standardized treatment algorithms and virtually complete follow-up. The TEAM trial had very few exclusion criteria, among which there was no upper age limitation. This enabled us to study age-specific persistence.

Because enrollment in the TEAM trial was restricted to patients with postmenopausal hormone receptor–positive disease, these results may not be extrapolated to all breast cancer patients. In addition, Ziller et al. [34] reported on the inconsistency between self-reported adherence and true adherence based on a retrospective prescription check. Moreover, a recent study by Hershman et al. [20] showed that 28% of patients on endocrine treatment who were persistent at 4.5 years of follow-up were nonadherent. These results indicate that persistence may not be as sensitive as adherence, especially when adherence is calculated by pharmacy data or prescriptions. In this report, we investigated nonpersistence. However, we were unable to assess adherence in patients who were persistent; therefore, we cannot exclude that persistence may have been influenced by adherence.

CONCLUSION

This study shows a higher proportion of adjuvant endocrine therapy nonpersistence within 1 year of follow-up in older patients. Based on these data and study design we are unable to report on the efficacy of adjuvant endocrine therapy in elderly breast cancer patients. However, we did show that nonpersistence of adjuvant endocrine therapy within 1 year of follow-up was associated with breast cancer–specific survival and overall survival outcomes in postmenopausal patients aged <65 years, but not in patients aged 65–74 years or in patients aged ≥75 years. The results presented in this study suggest that extrapolation of outcomes from a young, homogeneous population to a heterogeneous elderly population may be insufficient. Age-specific breast cancer studies are needed to establish differential outcomes in young and elderly breast cancer patients.

ACKNOWLEDGMENTS

The authors would like to thank Pfizer and The Dutch Cancer Society (2007–3968).

AUTHOR CONTRIBUTIONS

Conception/Design: Willemien van de Water, Esther Bastiaannet, Elysée T.M. Hille, Anton J.M. de Craen, Gerrit-Jan Liefers, Rudi G.J. Westendorp

Provision of study material or patients: Elysée T.M. Hille, Elma M. Meershoek-Klein Kranenbarg, Hein Putter, Caroline M. Seynaeve, Robert Paridaens, Cornelis J.H. van de Velde

Collection and/or assembly of data: Elysée T.M. Hille, Elma M. Meershoek-Klein Kranenbarg, Caroline M. Seynaeve, Robert Paridaens, Cornelis J.H. van de Velde

Data analysis and interpretation: Willemien van de Water, Esther Bastiaannet, Hein Putter, Gerrit-Jan Liefers

Manuscript writing: Willemien van de Water, Anton J.M. de Craen, Rudi G.J. Westendorp, Esther Bastiaannet, Gerrit-Jan Liefers

Final approval of manuscript: Willemien van de Water, Esther Bastiaannet, Elysée T.M. Hille, Elma M. Meershoek-Klein Kranenbarg, Hein Putter, Caroline M. Seynaeve, Robert Paridaens, Anton J.M. de Craen, Gerrit-Jan Liefers, Rudi G.J. Westendorp, Cornelis J.H. van de Velde

REFERENCES

- Jemal A, Bray F, Center MM et al. Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet* 2005;365:1687–1717.
- Chlebowski RT, Geller ML. Adherence to endocrine therapy for breast cancer. *Oncology* 2006;71:1–9.
- Fink AK, Gurwitz J, Rakowski W et al. Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor–positive breast cancer. *J Clin Oncol* 2004;22:3309–3315.
- Barron TI, Connolly R, Bennett K et al. Early discontinuation of tamoxifen: A lesson for oncologists. *Cancer* 2007;109:832–839.
- Demissie S, Silliman RA, Lash TL. Adjuvant tamoxifen: Predictors of use, side effects, and discontinuation in older women. *J Clin Oncol* 2001;19:322–328.
- Owusu C, Buist DS, Field TS et al. Predictors of tamoxifen discontinuation among older women with estrogen receptor–positive breast cancer. *J Clin Oncol* 2008;26:549–555.
- Ruddy KJ, Partridge AH. Adherence with adjuvant hormonal therapy for breast cancer. *Ann Oncol* 2009;20:401–402.
- Wildiers H, Kunkler I, Biganzoli L et al. Management of breast cancer in elderly individuals: Recommendations of the International Society of Geriatric Oncology. *Lancet Oncol* 2007;8:1101–1115.
- Hillner BE, Mandelblatt J. Caring for older women with breast cancer: Can observational research fill the clinical trial gap? *J Natl Cancer Inst* 2006;98:660–661.
- Van de Velde CJ, Rea D, Seynaeve C et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): A randomised phase 3 trial. *Lancet* 2011;377:321–331.
- Van Nes JG, Seynaeve C, Jones S et al. Variations in locoregional therapy in postmenopausal patients with early breast cancer treated in different countries. *Br J Surg* 2010;97:671–679.
- Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. *J Clin Oncol* 1983;1:710–719.
- Dezentjé VO, van Blijderveen NJ, Gelderblom H et al. Effect of concomitant CYP2D6 inhibitor use and tamoxifen adherence on breast cancer recurrence in early-stage breast cancer. *J Clin Oncol* 2010;28:2423–2429.
- Coombes RC, Kilburn LS, Snowdon CF et al. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Inter-group Exemestane Study): A randomised controlled trial. *Lancet* 2007;369:559–570.
- Howell A, Cuzick J, Baum M et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;365:60–62.
- Fisher B, Dignam J, Bryant J et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor–positive tumors. *J Natl Cancer Inst* 1996;88:1529–1542.
- Cuzick J, Forbes J, Edwards R et al. First results from the International Breast Cancer Intervention Study (IBIS-I): A randomised prevention trial. *Lancet* 2002;360:817–824.
- Fisher B, Costantino JP, Wickerham DL et al.

Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998; 90:1371–1388.

20. Hershman DL, Kushi LH, Shao T et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. *J Clin Oncol* 2010;28:4120–4128.

21. Partridge AH, Wang PS, Winer EP et al. Non-adherence to adjuvant tamoxifen therapy in women with primary breast cancer. *J Clin Oncol* 2003;21: 602–606.

22. Benner JS, Glynn RJ, Mogun H et al. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002;288:455–461.

23. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487–497.

24. Leventhal H, Nerenz DR, Leventhal EA et al. The behavioral dynamics of clinical trials. *Prev Med* 1991;20:132–146.

25. Urquhart J. Compliance and clinical trials. *Lancet* 1991;337:1224–1225.

26. Balkrishnan R. Predictors of medication adherence in the elderly. *Clin Ther* 1998;20:764–771.

27. Sharkness CM, Snow DA. The patient's view of hypertension and compliance. *Am J Prev Med* 1992;8:141–146.

28. Monane M, Bohn RL, Gurwitz JH et al. Noncompliance with congestive heart failure therapy in the elderly. *Arch Intern Med* 1994; 154:433–437.

29. Barat I, Andreassen F, Damsgaard EM. Drug therapy in the elderly: What doctors believe and patients actually do. *Br J Clin Pharmacol* 2001;51: 615–622.

30. Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med* 1990;150:841–845.

31. Coons SJ, Sheahan SL, Martin SS et al. Predictors of medication noncompliance in a sample of older adults. *Clin Ther* 1994;16:110–117.

32. Lichtman SM, Wildiers H, Launay-Vacher V et al. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. *Eur J Cancer* 2007;43:14–34.

33. Farmacotherapeutisch Kompas. 2011. 18–2-2011. Available at <http://fk.cvz.nl>, accessed June 1, 2011.

34. Ziller V, Walder M, Albert US et al. Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer. *Ann Oncol* 2009; 20(3):431–436.