Acta Oncologica, 2012; 51: 1036–1044

informa
healthcare

ORIGINAL ARTICLE

Persistent pain, sensory disturbances and functional impairment after adjuvant chemotherapy for breast cancer: Cyclophosphamide, epirubicin and fluorouracil compared with docetaxel + epirubicin and cyclophosphamide

KENNETH GEVING ANDERSEN[1], MAJ-BRITT JENSEN[2], HENRIK KEHLET[1], RUNE GÄRTNER[3], LISE ECKHOFF[4] & NIELS KROMAN[3]

[1]*Section for Surgical Pathophysiology, Rigshospitalet, Copenhagen University, Copenhagen, Denmark,* [2]*Danish Breast Cancer Cooperative Group, Rigshospitalet, Copenhagen, Denmark,* [3]*Department of Breast Surgery, Rigshospitalet, Copenhagen University, Copenhagen, Denmark, and* [4]*Department of Oncology, Odense University Hospital, University of Southern Denmark, Odense, Denmark*

Abstract

Background. Taxanes used in adjuvant therapy for breast cancer are neurotoxic, and thereby being a potential risk factor for persistent pain after breast cancer treatment (PPBCT) and sensory disturbances. The purpose was to compare patients treated with cyclophosphamide, epirubicin and fluorouracil (CEF) and cyclophosphamide and epirubicin + docetaxel (CE + T) in relation to PPBCT, sensory disturbances, peripheral sensory disturbances and functional impairment. *Material and methods.* A comparative nationwide cross-sectional questionnaire study on two cohorts treated with CEF respectively CE + T, based on the Danish Breast Cancer Cooperative Groups database. Inclusion criteria: women treated with chemotherapy as adjuvant treatment for primary breast cancer, age 18–69 years, without recurrence. *Results.* One thousand two hundred and forty-one patients allocated to CEF in 2005–2006 and 1652 patients allocated to CE + T in 2007–2008 were included. Six hundred and sixty-four (53%) with CEF and 861 (53%) patients with CE + T reported pain. In the multivariate analysis including available risk factors, CE + T did not confer an increased risk of PPBCT, OR 0.95 (95% CI 0.81–1.11), $p = 0.52$, compared to CEF. Patients treated with CE + T had a lower risk of sensory disturbances in the area of surgery compared with CEF, OR 0.75 (95% CI 0.62–0.90), $p = 0.002$. More CE + T patients reported peripheral sensory disturbances in the hands, OR 1.56 (95%CI 1.27–1.92), $p < 0.0001$, and in the feet, OR 2.0 (95% CI 1.66–2.42) $p < 0.0001$, compared to CEF. There was no difference in functional impairment ($p = 0.62$). *Conclusion.* Docetaxcel as adjuvant treatment for breast cancer does not increase the risk of PPBCT, sensory disturbances in the surgical area or functional impairment, but increase risk for peripheral sensory disturbances.

Several meta-analyses have shown that paclitaxel and docetaxel reduce the risk of recurrence and death after breast cancer by 20–30% and reduce the absolute risk of recurrence and death after five years by 5% and 3%, respectively [1–4]. This made the Danish Breast Cancer Cooperative Group (DBCG) introduce docetaxel (Taxotere®) into the adjuvant setting in the beginning of 2007 by adding three cycles of docetaxel subsequent to three cycles of epirubicin and cyclophosphamide (CE + T) replacing a treatment protocol with seven cycles cyclophosphamide, epirubicin and fluorouracil (CEF). Chemotherapy-induced neuropathy is a common side effect of several cytotoxic agents such as vinca alkaloids, platinum agents and taxanes, and affects the nervous system via different pathophysiological mechanisms [5,6]. Taxanes may induce a predominantly peripheral sensory neuropathy associated with numbness and paresthesias, often described by patients as stocking and glove sensation [5]. However, detailed knowledge about taxane induced neuropathy after breast cancer treatment is lacking due to small studies with a high degree of heterogeneity [7]. Furthermore, the neurotoxicity exerted by taxanes may be important in breast cancer, where persistent pain after breast cancer treatment (PPBCT) affects

Correspondence: K. G. Andersen, Section for Surgical Pathophysiology, 4074 Rigshospitalet, Copenhagen University, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. Tel: +45 35454236/+45 26258003. Fax: +45 35457157. E-mail: kenneth.geving.andersen@rh.regionh.dk

(Received 13 March 2012; accepted 4 May 2012)

ISSN 0284-186X print/ISSN 1651-226X online © 2012 Informa Healthcare
DOI: 10.3109/0284186X.2012.692884

between 25–60% of the patients and sensory disturbances in the area of surgery is reported by 31–85% depending on which treatment the patients have received [8]. A recent review of the PPBCT literature indicates a complex pathophysiology with several pre-, intra- and postoperative risk factors [9], including young age, axillary lymph node dissection (ALND) and radiation therapy as the most influential [9]. The influence of chemotherapy on PPBCT pathophysiology is poorly defined, mainly because of the lack of detailed information on type of treatment and proper stratification according to surgical and adjuvant treatment [9]. We have previously reported that CEF had no influence on PPBCT in a nationwide study on prevalence and risk factors for PPBCT and sensory disturbances in the surgical area [8]. The purpose of this study was therefore to compare a nationwide cohort, treated with CE + T with the nationwide cohort treated with CEF, in order to assess differences of the: 1) prevalence and characteristics of PPBCT and sensory disturbances in surgical area to clarify any role of chemotherapeutics in PPBCT pathophysiology; 2) prevalence of symptoms of symmetric peripheral sensory disturbances; and 3) functional impairment to evaluate the consequences of any differences.

Material and methods

The study is a comparative nationwide cross-sectional questionnaire study, comparing a cohort allocated to seven series of CEF for breast cancer in 2005–2006, hereafter referred to as the CEF cohort, with a cohort allocated to three series of CE followed by three series of docetaxel for breast cancer in 2007–2008, hereafter referred to as the CE + T cohort. Patients were identified in the national database managed by DBCG, which prospectively collects detailed clinical data, including disease characteristics and treatment [10,11], enabling eligible breast cancer patients treated in Denmark in the period to be contacted. Collection of data was done in a uniform manner and at two occasions. The study was approved by the Regional Bioethics committee of the capital region in Denmark, H-1-2010-028 and the Danish Data Protection Agency. The study is registered in clinicaltrials.gov, NCT01279018.

Population

Patients were identified in the DBCG database, with identical inclusion criteria in both cohorts: women aged between 18–69 years, primary operable breast cancer, who received chemotherapy for unilateral disease between 2005 and 2008. Exclusion criteria for both cohorts were contraindication to treatment according to the DBCG treatment protocol, reconstructive or cosmetic surgery, contralateral- recurrent-, new primary cancer, distant metastasis and other malignancy. Data on the CEF cohort was obtained from a larger cohort including all patients treated for breast cancer between 2005 and 2006, as described elsewhere [8]. Data collection on the CE + T cohort started on 11 November 2010, where a questionnaire identical to the one used in the CEF cohort was sent out. Patients not responding to the first inquiry received a reminder on 6 December 2011 and the data collection closed on 6 January 2011.

Treatment

The surgical treatment was performed according to DBCG guidelines and was the same between the two cohorts and included either mastectomy or breast conserving surgery (BCS) with either sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) levels I and II. The guidelines for allocation to radiotherapy, was the same between the cohorts. The CEF cohort received seven series of CEF according to the DBCG04 protocol. The CE + T cohort received treatment according to the DBCG07 protocol. Both protocols were based on the recommendation from the International Expert Consensus on Primary Therapy of Early Breast Cancer in 2003 [12] and 2005 [13], respectively. The CE + T cohort received sequential chemotherapy with three week intervals with three series of epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 followed by three series of docetaxel 100 mg/m^2. Patients with hormone receptor positive tumor were offered endocrine treatment. Premenopausal patients were offered tamoxifen, while postmenopausal patients were offered 2.5 years with tamoxifen followed by 2.5 years with an aromatase inhibitor.

Outcomes

The study questionnaire developed for the assessment of PPBCT, sensory disturbances and functional impairment in the 2005–2006 cohort [8,14] was used again to ensure comparability. This questionnaire uses accepted means of measure pain [15], and was content validated in the breast cancer population [8]. The primary outcome was the risk associated to the use of docetaxel, expressed as an odds ratio, for the development of PPBCT assessed in a model containing data from both cohorts. PPBCT was defined as presence of pain in the breast, side of chest, axilla or arm on the operated side more than 12 months after surgery. Secondary outcomes were intensity and frequency of pain in the four localizations, sensory disturbances in the surgical area, sensory disturbances in the hands and feet, and functional impairment. Questions addressing

prevalence of pain were assessed dichotomously with yes/no questions. Patients were then asked systematically to specify pain according localization, intensity and frequency. Intensity was assessed on a 0–10 numerical rating scale (NRS) and reported as light pain NRS 1–3, moderate pain NRS 4–7 and severe pain NRS 8–10. Frequency was assessed on a 3-point verbal scale: 1) every day or almost every day; 2) one to three days a week; 3) more rarely. Sensory disturbances were assessed by a dichotomous yes/no question, and the localization was specified. Symmetric peripheral sensory disturbance was assessed by asking if the patient experienced pain, sensory disturbance or discomfort in the hands and in the feet, and then whether this was present in both sides. Symmetric peripheral sensory disturbances were regarded present if symptoms were present both sides. Functional impairment was assessed by asking whether or not the patient have had to give up any activities because of the treatment. Treatment data were provided from the DBCG. Data on mortality were provided by the Danish Civil Registration System and data on patients who had received reconstructive surgery were acquired from the Danish National Patient Registry.

Statistics

The analysis of data was made by the DBCG data center. Multivariate logistic regression models were analyzed separately for each cohort to evaluate influence of age, surgical procedure, radiotherapy, endocrine therapy and time since surgery. Then the two cohorts were combined in models to examine the influence of docetaxel on pain, sensory disturbances in the surgical area, symmetric peripheral sensory disturbances in hands and feet and functional limitations. Using Proc Logistic in the SAS version 9.2 (SAS Institute, Cary, NC, USA), following factors were included: type of breast surgery (BCS vs. mastectomy), type of surgery in axilla ALND vs. SLNB, radiotherapy (breast radiotherapy (BRT)/anterior thoracic radiotherapy (ATRT) + locoregional radiotherapy (LRRT) vs. BRT vs. none), year of surgery, age, endocrine therapy (tamoxifen or aromatase inhibitor vs. none) and in the combined model: chemotherapy (CEF vs. CE + T). Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated, and Wald χ^2-test was used to test the overall significance of each parameter. All OR noted in the text are adjusted OR. Differences between pain intensity in the two cohorts (Table I) and localization of sensory disturbances were tested using the χ^2-test. Tests for interactions between the two cohorts and covariates on pain, sensory disturbances and functional impairment were done in separate models using Wald test statistics, and no interactions were found.

Results

Participants

One thousand two hundred and forty-one patients treated with CEF for breast cancer in Denmark between 2005–2006 fulfilled the inclusion criteria and responded to the questionnaire in 2008 (response rate 87%) [8]. Two thousand five hundred and fifty-four patients were enrolled into a protocol led treatment program with CE + T in Denmark from 2007 to 2008. Three hundred and thirteen were excluded because of reconstructive surgery, six patients had emigrated, and 206 patients were excluded because of recurrent cancer, contralateral breast cancer another malignancy or death. Two thousand and twenty-nine patients received the questionnaire. There were 365 non-responders, five declined to participate and seven patients who could not be reached. One thousand six hundred and fifty two questionnaires were included in the analysis, an overall response rate of 82% in the CE + T cohort. Thus, a total of 2893 patients from the two cohorts were included in the analysis.

Descriptive data

Mean ages at surgery was 49.8 years in the CEF cohort and 51.9 years in the CE + T cohort (p = 0.0001). Mean time from surgery to return of questionnaire was in the CEF cohort 25 months and in the CE + T cohort 34 months. The difference in follow-up was further analyzed in a sensitivity analysis, which did not change the estimates of any of the outcomes.

Pain

Six hundred and sixty-four (53%) in the CEF cohort and 861 (53%) patients in the CE + T cohort reported pain in the breast area, side of chest, axilla or arm on the operated side. Pain intensities and frequencies were similar (Table I). The multivariate analysis including age, type of surgery, time since surgery, radiotherapy, endocrine therapy and chemotherapy showed that docetaxel did not modify the risk of reporting PPBCT, OR 0.95 (95% CI 0.81–1.11), p = 0.52. Risk factors associated to PPBCT in both cohorts were young age, axillary lymph node dissection (ALND) and in the CE + T cohort also radiotherapy and shorter time since surgery (Table II).

Sensory disturbances in the breast area, side of chest, axilla and arm on the operated side

Of the patients in the CEF cohort, 851 (70%) and of the CE + T cohort 1034 (64%) reported sensory disturbances in the breast area, side of chest, axilla or arm on the operated side. Of patients reporting

Table I. Pain intensity and frequency in patients treated with chemotherapy in Denmark 2005–2008.

	CEF Cohort							CE+T Cohort						
	Light N	(%)	Moderate N	(%)	Severe N	(%)	Total N	Light N	(%)	Moderate N	(%)	Severe N	(%)	Total N
Breast area														
Every day or almost every day	114	(46)	107	(43)	27	(11)	248	148	(49)	121	(40)	34	(11)	303
1–3 times a week	94	(57)	67	(40)	5	(3)	166	122	(58)	84	(40)	3	(2)	209
More rarely	108	(77)	31	(22)	1	(1)	140	129	(69)	51	(27)	7	(4)	187
Total	316		205		33		554	399		256		44		699
Side of body														
Every day or almost every day	72	(45)	67	(42)	21	(13)	160	98	(48)	80	(39)	26	(13)	204
1–3 times a week	67	(55)	51	(41)	5	(4)	123	72	(53)	58	(42)	7	(5)	137
More rarely	63	(75)	20	(24)	1	(1)	84	87	(67)	38	(29)	5	(4)	130
Total	202		138		27		367	257		176		38		471
Axilla														
Every day or almost every day	79	(45)	66	(38)	29	(17)	174	103	(45)	94	(41)	33	(14)	230
1–3 times a week	69	(59)	40	(34)	8	(7)	117	90	(58)	58	(37)	7	(5)	155
More rarely	81	(76)	23	(21)	3	(3)	107	123	(80)	28	(18)	3	(2)	154
Total	229		129		40		398	316		180		43		539
Arm														
Every day or almost every day	64	(32)	87	(44)	48	(24)	199	72	(29)	118	(47)	61	(24)	251
1–3 times a week	53	(51)	44	(43)	6	(6)	103	70	(50)	62	(44)	8	(56)	140
More rarely	55	(73)	18	(24)	2	(3)	75	67	(66)	33	(33)	1	(1)	101
Total	172		149		56		377	209		213		70		492

Pain intensity reported on a 0–10 numerical rating scale (NRS). Light pain, NRS 1–3; moderate pain, NRS 4–7; severe pain, 8–10.

Table II. Pain among breast cancer patients treated with adjuvant chemotherapy in Denmark 2005–2008 adjusted for age, type of surgery, radiotherapy, endocrine therapy and follow-up.

		CEF cohort							CE +T cohort						
		+ Pain N	(%)	-Pain N	(%)	Adj OR	95% CI	P-value	+ Pain N	(%)	- Pain N	(%)	Adj. OR	95% CI	P-value
Total		664	(53)	556	(67)				861	(53)	770	(67)			
Age	≤39	88	(65)	47	(35)	2.52	1.55; 4.12	0.0005	69	(56)	55	(44)	1.67	1.03; 2.69	0.03
	40–49	301	(59)	208	(41)	1.96	1.31; 2.92		267	(58)	196	(42)	1.68	1.14; 2.47	
	50–59	200	(51)	194	(49)	1.41	0.97; 2.05		438	(53)	396	(47)	1.33	0.93; 1.92	
	60–69	75	(41)	107	(59)	1			87	(41)	123	(59)	1		
Surgery															
Breast	Mastectomy	246	(53)	219	(47)	0.84	0.60; 1.18	0.33	288	(50)	286	(50)	0.90	0.67; 1.20	0.46
	BCS	418	(55)	337	(45)	1			573	(54)	484	(46)	1		
Axilla	ALND	450	(58)	320	(42)	1.57	1.10; 2.24	0.01	604	(57)	450	(43)	1.46	1.08; 1.98	0.01
	SLNB	214	(48)	236	(52)	1			257	(45)	320	(55)	1		
RT	LRRT + BRT/ATRT	335	(59)	233	(41)	1.14	0.75; 1.73	0.82	457	(59)	314	(41)	1.83	1.26; 2.65	0.007
	BRT	247	(52)	229	(48)	1.14	0.69; 1.89		320	(50)	319	(50)	1.58	1.02; 2.45	
	None	82	(47)	94	(53)	1			84	(38)	137	(62)	1		
ET	+	378	(58)	276	(42)	0.96	0.74; 1.26	0.78	610	(56)	489	(44)	1.09	0.85; 1.41	0.48
	-	286	(51)	280	(49)	1			251	(47)	281	(53)	1		
Year of surgery	2005/2007	317	(54)	272	(46)	0.94	0.74; 1.18	0.58	371	(50)	366	(50)	0.81	0.67; 0.99	0.04
	2006/2008	347	(55)	284	(45)	1			490	(55)	404	(45)	1		

ALND, axillary lymph node dissection; ATRT, anterior thoracic radiotherapy corresponding to anterior thoracic wall; BCS, breast conserving surgery; BRT, breast radiotherapy corresponding to residual breast tissue; ET, endocrine therapy with either tamoxifen or aromatase inhibitor; LRRT, locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right side cancers, the internal mammary nodes; RT, radiotherapy; SLNB, sentinel lymph node biopsy; Year of surgery, patients treated in 2005 vs. 2006 for the CEF cohort, and 2007 vs. 2008 for the CE +T cohort.

Table III. Sensory disturbances in the surgical area among breast cancer patients treated with adjuvant chemotherapy in Denmark 2005–2008 adjusted for age, type of surgery, radiotherapy, endocrine therapy and follow-up.

		CEF cohort					CE + T cohort				
		+ Sensory dist. N (%)	− Sensory dist. N (%)	Adj. OR	95%CI	P-value	+ Sensory dist. N (%)	-Sensory dist. N (%)	Adj. OR	95%CI	P-value
Total		851 (70)	367 (30)				1034 (64)	580 (36)			
Age	≤ 39	113 (84)	22 (16)	4.14	2.24; 7.63	<.0001	90 (72)	35 (28)	2.85	1.65; 4.90	< 0.0001
	40–49	377 (75)	127 (25)	2.07	1.32; 3.25		336 (73)	127 (27)	2.45	1.59; 3.77	
	50–59	263 (66)	135 (34)	1.41	0.93; 2.13		507 (62)	317 (38)	1.27	0.86; 1.89	
	60–69	98 (54)	83 (46)	1			101 (50)	101 (50)	1		
Surgery											
Breast	Mastectomy	364 (77)	110 (23)	0.78	0.50; 1.21	0.27	407 (72)	161 (28)	0.87	0.61; 1.23	0.43
	BCS	487 (65)	257 (35)	1			627 (60)	419 (40)	1		
Axilla	ALND	650 (84)	128 (16)	5.92	3.82; 9.19	<.0001	807 (77)	243 (23)	3.70	2.67; 5.13	< 0.0001
	SLNB	201 (46)	239 (54)	1			227 (40)	337 (60)	1		
RT	LRRT + BRT/ATRT	478 (83)	96 (17)	0.62	0.36; 1.06	0.08	600 (78)	168 (22)	0.93	0.60; 1.43	0.007
	BRT	247 (53)	216 (47)	0.51	0.28; 0.94		296 (47)	333 (53)	0.53	0.32; 0.86	
	None	126 (70)	55 (30)	1			138 (64)	79 (36)	1		
ET	+	495 (76)	158 (24)	1.18	0.86; 1.62	0.32	745 (68)	350 (32)	1.26	0.95; 1.67	0.10
	-	356 (63)	209 (37)	1			289 (56)	230 (44)	1		
Year of surgery	2005/2007	410 (70)	177 (30)	0.93	0.71; 1.22	0.60	448 (62)	279 (38)	0.81	0.64; 1.01	0.06
	2006/2008	441 (70)	190 (30)	1			586 (66)	301 (34)	1		

ALND, axillary lymph node dissection; ATRT, anterior thoracic radiotherapy corresponding to anterior thoracic wall; BCS, breast conserving surgery; BRT, breast radiotherapy corresponding to residual breast tissue; ET, endocrine therapy with either tamoxifen or aromatase inhibitor; LRRT, locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right side cancers, the internal mammary nodes; RT, radiotherapy; SLNB, sentinel lymph node biopsy; Year of surgery, patients treated in 2005 vs. 2006 for the CEF cohort, and 2007 vs. 2008 for the CE + T cohort.

sensory disturbances, this was most prevalent in the axilla (67%) and the arm on the operated side (56%). There were no significant differences between the cohorts on localization of sensory disturbances. In the multivariate analysis young age and ALND were found as risk factors in both cohorts (Table III). Patients treated with docetaxel had a significantly lower risk of reporting sensory disturbances, OR 0.75 (95% CI 0.62–0.90, $p = 0.002$).

Symmetric peripheral sensory disturbances in hands/fingers and feet/toes

In the CEF cohort 175 (15%) patients reported sensory disturbances in both hands, compared to 363 (23%) among patients in the CE + T cohort. In the multivariate model, docetaxel was associated with a higher risk of peripheral sensory disturbance in the hands, OR 1.56 (95% CI 1.27–1.92, $p < 0.0001$). In the CE + T there was a significant association with age ($p = 0.002$) with a higher risk for patients aged 50–59 years, and lower for patients aged under 40 (Table IV). Correspondingly, 213 (18%) patients in the CEF cohort reported symmetric peripheral sensory disturbances in the feet, compared with 506 (32%) in the CE + T cohort. In the combined model, docetaxel was associated with a significantly higher risk of peripheral sensory disturbance in the feet with an OR of 2.00 (95% CI 1.66–2.42, $p < 0.0001$). Age was also a significant risk factor for peripheral sensory disturbances in the feet in the CE + T cohort with less disturbances among younger patients, OR 0.45 (95% CI 0.26–0.77). In the CEF cohort, endocrine treatment was found as a risk factor for reporting peripheral sensory disturbances in the feet OR 1.53 (95% CI 1.07–2.20, $p = 0.02$) (Table V).

Functional impairment

In the CEF cohort 405 patients (34%), and in the CE + T cohort 535 (34%) reported functional impairment defined as having to give up activities because of the treatment. In both cohorts significant risk factors for giving up activities were younger age and ALND. In the CE + T cohort, mastectomy was related to a higher risk of giving up activities, OR

Table IV. Peripheral sensory disturbances in hands among breast cancer patients treated with adjuvant chemotherapy in Denmark 2005–2008 adjusted for age, type of surgery, radiotherapy, endocrine therapy and follow-up.

		CEF cohort					CE + T cohort				
		+ Pain N (%)	− Pain N (%)	Adj OR	95% CI	P-value	+ Pain N (%)	− Pain N (%)	Adj. OR	95% CI	P-value
Total		175 (15)	1026 (85)				363 (23)	1233 (77)			
Age	≤ 39	13 (10)	121 (90)	0.84	0.38;1.86	0.14	21 (17)	105 (83)	0.70	0.38;1.30	0.002
	40–49	80 (16)	418 (84)	1.46	0.79;2.70		85 (19)	374 (81)	0.78	0.48;1.27	
	50–59	64 (16)	328 (84)	1.58	0.88;2.84		216 (27)	592 (73)	1.28	0.82;2.00	
	60–69	18 (10)	159 (90)	1			41 (20)	162 (80)	1		
Surgery											
Breast	Mastectomy	67 (14)	397 (86)	0.97	0.60;1.55	0.89	119 (21)	437 (79)	0.94	0.66;1.33	0.71
	BCS	108 (15)	629 (85)	1			244 (23)	796 (77)	1		
Axilla	ALND	109 (14)	650 (86)	0.85	0.51;1.41	0.52	223 (22)	812 (78)	0.82	0.58;1.17	0.28
	SLNB	66 (15)	376 (85)	1			140 (25)	421 (75)	1		
RT	LRRT + BRT/ATRT	82 (15)	480 (85)	0.98	0.54;1.78	0.91	161 (21)	593 (79)	0.92	0.59;1.45	0.93
	BRT	67 (15)	395 (85)	0.87	0.44;1.75		154 (24)	476 (76)	0.98	0.58;1.64	
	None	26 (15)	151 (85)	1			48 (23)	164 (77)	1		
ET	+	105 (16)	543 (84)	1.25	0.86;1.83	0.24	258 (24)	823 (76)	1.24	0.91;1.69	0.18
	−	70 (13)	483 (87)	1			105 (20)	410 (80)	1		
Year of surgery	2005/2007	83 (14)	498 (86)	0.95	0.69;1.32	0.76	153 (21)	567 (79)	0.84	0.66;1.07	0.16
	2006/2008	92 (15)	528 (85)	1			210 (24)	666 (76)	1		

ALND, axillary lymph node dissection; ATRT, anterior thoracic radiotherapy corresponding to anterior thoracic wall; BCS, breast conserving surgery; BRT, breast radiotherapy corresponding to residual breast tissue; ET, endocrine therapy with either tamoxifen or aromatase inhibitor; LRRT, locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right side cancers, the internal mammary nodes; RT, radiotherapy; SLNB, sentinel lymph node biopsy.

1.59, 95% CI 1.18–2.14, p = 0.02 (see Table VI). In the combined model, docetaxel did not represent any additional risk of functional impairment, OR 1.04 (95% CI 0.88–1.24, p = 0.62)

Discussion

The results of this nationwide study suggest that the addition of docetaxel to adjuvant chemotherapy has not changed the prevalence or pattern of PPBCT, and is similar to the CEF regime with regard to dimensions of pain such as intensity, frequency and localization. Furthermore, this study confirms that PPBCT is one of the major late effects of treatment for breast cancer, and affects more than half of the patients two to three years after surgery. The pattern of PPBCT in relation to the different treatment modalities was similar for the present cohort to the cohort treated in 2005–2006 [8] and agrees well with the risk factors identified in the literature [9]. Sensory disturbances in area of surgery were reported by relatively fewer patients in the docetaxel cohort, with a statistically significant OR of 0.75. This difference is not easily explained, as there is no obvious pathophysiological reason for any positive effect of docetaxel with regard to sensory disturbances. The difference in time since surgery could be proposed as a reason for this. However, a subgroup analysis and tests for interactions shows the difference in time since surgery is not confounding the result for sensory disturbances nor any of the other outcomes. It may however be explained by response-shift bias. Response shift bias is commonly occurring in quality of life studies, and refers to the phenomenon when self reported constructs change over time due to change of internal standards, values and reconceptualization of health state due to a change in health state [16]. Patients treated with docetaxel have more extensive short-term side effects due to the treatment as measured on global health status [17], pain and peripheral sensory neuropathy [18,19] and may thus be more susceptible to a response shift bias. In conclusion, these results suggest that docetaxel in combination with CE, does not increase the risk of developing PPBCT or sensory disturbances in the surgical area.

Table V. Peripheral sensory disturbances in feet among breast cancer patients treated with adjuvant chemotherapy in Denmark 2005–2008 adjusted for age, type of surgery, radiotherapy, endocrine therapy and follow-up.

		CEF cohort							CE + T cohort						
		+ Periph. SD N	(%)	− Periph. SD N	(%)	Adj. OR	95% CI	P-value	+ Periph. SD N	(%)	− Periph. SD N	(%)	Adj. OR	95% CI	P-value
Total		213	(18)	979	(82)				506	(32)	1090	(78)			
Age	≤ 39	15	(11)	121	(89)	0.56	0.27;1.16	0.07	26	(21)	100	(79)	0.45	0.26;0.77	0.02
	40–49	95	(19)	405	(81)	1.01	0.58;1.77		140	(31)	317	(69)	0.74	0.49; 1.12	
	50–59	78	(20)	306	(80)	1.24	0.74;2.11		270	(33)	543	(67)	0.83	0.57;1.23	
	60–69	25	(15)	147	(85)	1			70	(35)	130	(65)	1		
Surgery															
Breast	Mastectomy	74	(16)	384	(84)	0.88	0.57;1.35	0.55	174	(31)	379	(69)	0.95	0.70;1.29	0.74
	BCS	139	(19)	595	(81)	1			332	(32)	711	(68)	1		
Axilla	ALND	128	(17)	632	(83)	0.65	0.40;1.06	0.09	323	(31)	712	(69)	0.79	0.57;1.10	0.16
	SLNB	85	(20)	347	(80)	1			183	(33)	378	(67)	1		
RT	LRRT + BRT/ATRT	100	(18)	465	(82)	1.30	0.72;2.33	0.52	242	(32)	509	(68)	1.10	0.74;1.65	0.50
	BRT	87	(19)	369	(81)	0.99	0.51;1.92		197	(31)	435	(69)	0.89	0.56;1.41	
	None	26	(15)	145	(85)	1			67	(31)	146	(69)	1		
ET	+	132	(20)	518	(80)	1.53	1.07;2.20	0.02	348	(32)	735	(68)	1.17	0.89;1.55	0.26
	−	81	(15)	461	(85)	1			158	(31)	355	(69)	1		
Year of surgery	2005/2007	110	(19)	468	(81)	1.18	0.88;1.60	0.27	217	(30)	502	(70)	0.87	0.71;1.08	0.22
	2006/2008	103	(17)	511	(83)	1			289	(33)	588	(67)	1		

ALND, axillary lymph node dissection; ATRT, anterior thoracic radiotherapy corresponding to anterior thoracic wall; BCS, breast conserving surgery; BRT, breast radiotherapy corresponding to residual breast tissue; ET, endocrine therapy with either tamoxifen or aromatase inhibitor; LRRT, locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right side cancers, the internal mammary nodes; RT, radiotherapy; SLNB, sentinel lymph node biopsy; Year of surgery, patients treated in 2005 vs. 2006 for the CEF cohort, and 2007 vs. 2008 for the CE + T cohort.

Our screening for symmetric peripheral sensory disturbances found these symptoms present in 23% of the patients in the hands and 32% in the feet in the CE + T cohort, which was significantly more than reported among patients in the CEF cohort. The results may be overestimated, as the question used to screen for peripheral sensory disturbances is simple, and consequently without the specificity of a validated questionnaire. The difference between the CEF and CE + T cohort are however similar to the results reported by Martin et al., where 15% of the patients treated with taxotere, anthracycline and cyclophosphamide compared to 7% of patients treated with fluorouracil, anthracycline and cyclophosphamide are reported to have sensory neuropathy during the treatment [19]. Long-term follow-up data on peripheral neuropathy after treatment with docetaxel is scarce in the literature. However, Hershman et al. found that 81% reported discomfort in the hands and or feet, with 27% reporting severe symptoms in the hands 6–24 months after treatment with paclitaxel in a cross-sectional study [20]. In a prospective component of the same study, 67% reported persisting numbness in hands or feet at 12 months [20]. The higher prevalence in the study be Hershman et al. and our data may be attributed a difference between paclitaxel and docetaxel, differences in assessment, as well as a relatively low number of patients enrolled (N = 50 in both the cross-sectional and prospective cohort). However, our data provide indications that peripheral sensory disturbances due to treatment with docetaxel probably represent a long-term problem. A clinical implication of this with a higher degree of functional impairment after treatment with docetaxel could not be found in our screening of functional impairments, and the risk factor profile of the two cohorts were similar. There may however be subtle changes in specific aspects of function, such as buttoning a button, which we cannot conclude on.

Neurotoxicity is a dose limiting factor with docetaxel, although this drug has not been studied as extensively paclitaxel. The effects of docetaxel are reported to be milder than paclitaxel and the neurotoxicity may be caused by other targets such as the dorsal root ganglia [5]. The neurotoxicity exerted by

Table VI. Functional impairment among breast cancer patients treated with adjuvant chemotherapy in Denmark 2005–2008 adjusted for age, type of surgery, radiotherapy, endocrine therapy and follow-up.

		CEF cohort					CE+T cohort				
		+Pain N (%)	−Pain N (%)	Adj OR	95% CI	P-value	+Pain N (%)	−Pain N (%)	Adj. OR	95% CI	P-value
Total		405 (34)	783 (66)				535 (34)	1044 (66)			
Age	≤39	55 (41)	79 (59)	2.65	1.53; 4.59	0.004	49 (40)	74 (60)	2.13	1.26; 3.60	0.0002
	40–49	184 (37)	308 (63)	2.18	1.35; 3.50		182 (40)	268 (60)	2.11	1.37; 3.26	
	50–59	131 (34)	255 (66)	1.97	1.25; 3.10		254 (32)	549 (68)	1.37	0.91; 2.07	
	60–69	35 (20)	141 (80)	1			50 (25)	153 (75)	1		
Surgery											
Breast	Mastectomy	183 (40)	269 (60)	1.03	0.73; 1.44	0.88	223 (40)	329 (60)	1.59	1.18; 2.14	0.02
	BCS	222 (30)	514 (70)	1			312 (30)	715 (70)	1		
Axilla	ALND	309 (41)	436 (59)	1.77	1.20; 2.61	0.004	414 (41)	602 (59)	2.27	1.63; 3.15	<0.0001
	SLNB	96 (22)	347 (78)	1			121 (21)	442 (79)	1		
RT	LRRT+ BRT/ATRT	236 (43)	316 (57)	0.90	0.58; 1.38	<0.05	164 (26)	459 (74)	1.57	1.06; 2.33	0.06
	BRT	105 (23)	358 (77)	0.55	0.33; 0.93		309 (42)	432 (58)	1.67	1.04; 2.67	
	None	64 (37)	109 (63)	1			62 (29)	153 (71)	1		
ET	+	243 (38)	393 (62)	1.08	0.81; 1.44	0.61	378 (35)	688 (65)	0.94	0.71; 1.23	0.63
	−	162 (29)	390 (71)	1			157 (31)	356 (69)	1		
Year of surgery	2005/2007	206 (36)	360 (64)	1.22	0.95; 1.56	0.12	238 (33)	480 (67)	0.97	0.78; 1.20	0.76
	2006/2008	199 (32)	423 (68)	1			297 (34)	564 (66)	1		

ALND, axillary lymph node dissection; ATRT, anterior thoracic radiotherapy corresponding to anterior thoracic wall; BCS, breast conserving surgery; BRT, breast radiotherapy corresponding to residual breast tissue; ET, endocrine therapy with either tamoxifen or aromatase inhibitor; FI, functional impairment; LRRT, locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right side cancers, the internal mammary nodes; RT, radiotherapy; SLNB, sentinel lymph node biopsy; Year of surgery, patients treated in 2005 vs. 2006 for the CEF cohort, and 2007 vs. 2008 for the CE+T cohort.

paclitaxel is reported to be axonal atrophy with absence of axonal regeneration and secondary demyelination [5]. Furthermore, animal studies have shown a shift towards smaller fibers [21], which is interesting with regards to chronic pain. These results can therefore not be generalized to taxanes as a group, and further studies are required on patients treated with paclitaxel.

The strengths of this study include that it is based on the population treated with adjuvant chemotherapy according to the guidelines for breast cancer in Denmark from 2005–2008. The data collection was performed with the same questionnaire for both cohorts yielding a high response rate in both cohorts, and thereby minimizing selection bias. Furthermore, the large size of each cohort allowed a calculation of risk factors within each cohort and between cohorts with sufficient precision to detect clinically relevant differences.

Limitations are the cross-sectional design without base line information, which precludes conclusions on causality and the dynamics of the symptoms reported. Furthermore, in terms of sensory disturbances and symmetric sensory disturbances, the questionnaire used is not validated against other questionnaires measuring neuropathic signs and symptoms, which makes the results less comparable to other studies. Finally, smoking habits and co-morbidities such as diabetes were not recorded, which potentially could introduce a bias, if there was a difference of the prevalence of these factors between the cohorts.

Conclusion

This large nationwide study supports that PPBCT remains a significant problem among breast cancer survivors with young age, radiotherapy and axillary lymph node dissection being the main risk factors for developing PPBCT. The introduction of docetaxel in the adjuvant treatment of breast cancer has not changed the prevalence and pattern of PPBCT, but prevalence of sensory disturbances in the hands and feet are increased and may be a long-term problem. Future studies of PPBCT should be prospective, including quantitative sensory testing, as well as details on surgical and radiation therapy, to evaluate the potential for reducing intercostobrachial nerve injury in surgery [9]

and radiation therapy [22], and provide more solid data on the time course of peripheral neuropathy. Several studies are underway in Denmark to further characterize docetaxel-induced neuropathy.

Acknowledgements

This study was supported by the Danish Cancer Society and is a part of the Europain project, funded by the Innovative Medicines Initiative Joint Undertaking (IMI JU) Grant no 115007 (www.imi.europa.eu).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Ferguson T, Wilcken N, Vagg R, Ghersi D, Nowak AK. Taxanes for adjuvant treatment of early breast cancer. Cochrane Database Syst Rev 2007;CD004421.

[2] Bria E, Nistico C, Cuppone F, Carlini P, Ciccarese M, Milella M, et al. Benefit of taxanes as adjuvant chemotherapy for early breast cancer: Pooled analysis of 15,500 patients. Cancer 2006;106:2337–44.

[3] De Laurentiis M, Cancello G, D'Agostino D, Giuliano M, Giordano A, Montagna E, et al. Taxane-based combinations as adjuvant chemotherapy of early breast cancer: A meta-analysis of randomized trials. J Clin Oncol 2008;26:44–53.

[4] Estevez LG, Munoz M, Alvarez I, Fernandez Y, Garcia-Mata J, Ruiz-Borrego M, et al. Evidence-based use of taxanes in the adjuvant setting of breast cancer. A review of randomized phase III trials. Cancer Treat Rev 2007;33:474–83.

[5] Balayssac D, Ferrier J, Descoeur J, Ling B, Pezet D, Eschalier A, et al. Chemotherapy-induced peripheral neuropathies: From clinical relevance to preclinical evidence. Expert Opin Drug Saf 2011;10:407–17.

[6] Park SB, Krishnan AV, Lin CS, Goldstein D, Friedlander M, Kiernan MC. Mechanisms underlying chemotherapy-induced neurotoxicity and the potential for neuroprotective strategies. Curr Med Chem 2008;15:3081–94.

[7] Eckhoff L, Nielsen M, Moeller S, Knoop A. TAXTOX: – A retrospective study regarding the side effects of docetaxel given as part of the adjuvant treatment to patients with primary breast cancer in Denmark from 2007 to 2009. Acta Oncol 2011;50:1075–82.

[8] Gartner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA 2009;302:1985–92.

[9] Andersen KG, Kehlet H. Persistent pain after breast cancer treatment: A critical review of risk factors and strategies for prevention. J Pain 2011;12:725–46.

[10] Blichert-Toft M, Christiansen P, Mouridsen HT. Danish Breast Cancer Cooperative Group – DBCG: History, organization, and status of scientific achievements at 30-year anniversary. Acta Oncol 2008;47:497–505.

[11] Moller S, Jensen MB, Ejlertsen B, Bjerre KD, Larsen M, Hansen HB, et al. The clinical database and the treatment guidelines of the Danish Breast Cancer Cooperative Group (DBCG); its 30-years experience and future promise. Acta Oncol 2008;47:506–24.

[12] Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Meeting highlights: Updated international expert consensus on the primary therapy of early breast cancer. J Clin Oncol 2003;21:3357–65.

[13] Goldhirsch A, Glick JH, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Meeting highlights: International expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 2005;16:1569–83.

[14] Gartner R, Jensen MB, Kronborg L, Ewertz M, Kehlet H, Kroman N. Self-reported arm-lymphedema and functional impairment after breast cancer treatment – a nationwide study of prevalence and associated factors. Breast 2010; 19:506–15.

[15] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9–19.

[16] Schwartz CE, Sprangers MA. Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. Soc Sci Med 1999;48:1531–48.

[17] Martin M, Lluch A, Segui MA, Ruiz A, Ramos M, Adrover E, et al. Toxicity and health-related quality of life in breast cancer patients receiving adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC): Impact of adding primary prophylactic granulocyte-colony stimulating factor to the TAC regimen. Ann Oncol 2006;17:1205–12.

[18] Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, Weaver C, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352:2302–13.

[19] Martin M, Segui MA, Anton A, Ruiz A, Ramos M, Adrover E, et al. Adjuvant docetaxel for high-risk, node-negative breast cancer. N Engl J Med 2010;363:2200–10.

[20] Hershman DL, Weimer LH, Wang A, Kranwinkel G, Brafman L, Fuentes D, et al. Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. Breast Cancer Res Treat 2011;125:767–74.

[21] Persohn E, Canta A, Schoepfer S, Traebert M, Mueller L, Gilardini A, et al. Morphological and morphometric analysis of paclitaxel and docetaxel-induced peripheral neuropathy in rats. Eur J Cancer 2005;41:1460–6.

[22] Andersen KG, Gartner R, Kroman N, Flyger H, Kehlet H. Persistent pain after targeted intraoperative radiotherapy (TARGIT) or external breast radiotherapy for breast cancer: A randomized trial. Breast 2012;21:46–9.