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CLINICAL TRIAL

Quality of life during and after adjuvant anthracycline-taxane-based chemotherapy with or without Gemcitabine in high-risk early breast cancer: results of the SUCCESS A trial

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Abstract

Purpose In high-risk early breast cancer, adjuvant taxane-Gemcitabine combinations result in a recurrence-free survival similar to single-agent taxanes. However, haematologic toxicities and need for dose reductions are more frequent in combinations. Which option ultimately provides a better quality of life (QoL) is unknown. We compared the QoL curves before, during, and up to one year after three cycles of Fluorouracil–epirubicin–cyclophosphamide followed by three cycles of Docetaxel–Gemcitabine or Docetaxel.

Methods Overall, 3691 women with recent R0-resection of a primary epithelial breast cancer participated in the nationwide SUCCESS A clinical trial. The centres sent QoL questionnaires of the European Organisation for Research and Treatment of Cancer before and up to 15 months after randomisation to Docetaxel–Gemcitabine versus Docetaxel. Multilevel analysis by chemotherapy arm estimated the QoL time curves, questionnaire return, and dropout.

Results The combination caused one-point higher global QoL (95% confidence ±1; $p=0.05$) and 1.1 lower odds of adherence to the outcome (95% confidence 1.0–1.1; $p=0.23$) than the monotherapy. In both groups, a 10-point decrease during therapy preceded a 16-point increase after chemotherapy ($p<0.001$). The secondary QoL outcomes showed transient superiority of the combination at the end of chemotherapy. Discontinuation from chemotherapy and its reasons were equal in both groups.

Conclusions While patients perceive a one-point QoL difference as meaningless, a six-point increase is clinically relevant for them. That is, both regimens cause the same relevant long-term QoL improvement. With the similar recurrence-free survival, the lower toxicity, and the shorter chemotherapy duration in mind, taxanes without Gemcitabine are the preference. This challenges previous recommendations supporting combinations.

Keywords Breast neoplasms · Quality of life · Toxoids · Anthracyclines · Gemcitabine

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Abbreviations

QoL	Quality of life
DG	Docetaxel–Gemcitabine
D	Docetaxel
FEC	Fluorouracil–Epirubicin–Cyclophosphamide
95% CI	95% confidence interval
EORTC QLQ-C30	30-Item core questionnaire of the European Organisation for Research and Treatment of Cancer

Introduction

With a 13% lifetime incidence risk [1], breast cancer is the most common malignancy in women [2], and their quality of life (QoL) suffers from this disease and its treatment [3]. In one-third of the cases [4], chemotherapy may alleviate the symptoms [5], and, for high-risk early breast cancer [6], reduce the 10-year recurrence by ≥ 5%. Gemcitabine is a pyrimidine analogue that stops the DNA elongation after adding a physiological nucleotide (masked termination). It competitively inhibits the DNA polymerase and the ribonucleotide reductase [7]. Phase II studies have reported 19% WHO-grade 3 and 3% WHO-grade 4 toxicities with Gemcitabine and 30% WHO-grade 3 and 11% of WHO-grade 4 toxicities with Docetaxel–Gemcitabine (DG) [8].

The unique triple action and moderate toxicity of Gemcitabine deserve particular attention in breast cancer. In the SUCCESS A trial, we found more women with hematologic toxicities such as thrombocytopenia (2% vs. 0%) and leukopenia (64% vs. 58%) with DG than with Docetaxel (D), both following fluorouracil–epirubicin–cyclophosphamide (FEC) [9]. Fifty-nine percent with FEC-DG versus 36% with FEC-D needed more granulocyte colony-stimulating factor, and 4% versus 2% needed dose reductions of more than 20%. Neuropathy (1% vs. 0%), arthralgia (2% vs. 1%), and bone pain (3% vs. 1%) were more frequent with FEC-D.

Recent neoadjuvant [10] and adjuvant breast cancer trials [11–13] challenge the superior recurrence-free survival of combinations over single-agents [14, 15], and the QoL still remains largely unexplored. A meta-analysis comparing combinations of taxanes and novel non-taxane agents, such as Vinorelbine, Gemcitabine, or Capecitabine, with single taxanes, reported a pooled hazard of 0.8 (95% confidence interval (CI) 0.7–0.9) favouring the combinations [15]. One of the rare [16] DG versus D trials found a hazard ratio of 0.8 for time-to-treatment failure [11], another found a hazard ratio of 0.9 for disease-free survival [12], and we found the same [13]. The former favoured the single agent, the latter two the combination, and all were statistically nonsignificant. None reported QoL.

One reason for the under-investigation of QoL in chemo versus chemo studies [17] might be that time-to-event outcomes are easier to analyse than QoL curves [18, 19]. Using the 0-to-100-point, 30-item core questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30), one study confirmed a previous finding [20] of an eight-point difference in global QoL at three months ($p = 0.001$) for a higher dosage compared to a longer FEC [21]. While another trial found better QoL with oral rather than with intravenous chemotherapy [22], most QoL breast cancer trials compared chemotherapy with hormone therapy, stem cell transplant, or surgery, or analysed QoL as a predictor rather than as an outcome [17].

This report compares the QoL of women with high-risk early breast cancer randomized to two different adjuvant chemotherapies, namely three cycles of FEC in both groups followed by three cycles of DG in one group versus three cycles of D in the other.

Methods

Design

From September 2005 to March 2007, 271 study centres across Germany coordinated the SUCCESS A trial (clinicaltrials.gov: NCT02181101). The centres informed the local gynaecologists and gynaecological oncologists about the trial, who then informed their potentially eligible patients orally and in writing. After confirming eligibility and obtaining written informed consent, they transmitted their patients´ contact information and baseline characteristics to the centre. The centre completed this information as necessary and, before therapy, sent the first QoL questionnaire (t1) to each participant's postal address. Varying recovery times might have prolonged the 21 days scheduled between each of the six chemotherapy cycles.

The centres sent the second (t2) and third (t3) QoL questionnaires after the 3rd and 6th cycles respectively and assigned the women to FEC-DG versus FEC-D arms before the 4th cycle. Further questionnaires followed 3 (t4), 6 (t5), 9 (t6), and 12 months (t7) after chemotherapy. The women were advised to complete the questionnaires at rest and independently, and they received stamped postal envelopes to return the completed questionnaires. To ensure quality, a clinical research organisation (CRO) regularly visited the centres and electronically managed the data, including automated plausibility checks. Led by the ethical board of the Ludwig-Maximilian-University of Munich, 37 local boards approved the study. The full protocol is available at http://www.success-studie.de/a/downloads.htm. The dataset generated and analysed during this study is available from the

steering committee of the SUCCESS A trial upon reasonable request.

Eligibility

Eligible women were ≥ 18 years old with a ≤ 6-week-old R0 resection of an invasive primary epithelial breast cancer without distant metastases. They had a high recurrence risk, namely age ≤ 35 years at diagnosis, multifocal, multicentric or bilateral cancer, stage ≥ T2 (> 2 cm), G3 differentiation, hormone receptor negative tissue, or lymph node metastases. Their condition on the scale of the Eastern Cooperative Oncology Group was ≤ 2 (i.e. capable of all selfcare), and they were able to understand the study concept well. They consented to regular aftercare. They had $\geq 3.0 \times 10^9$ leucocytes and $\geq 100 \times 10^9$ thrombocytes per blood litre, and their aspartate, alanine aminotransferase, and alkaline phosphatase were within 1.5 times the reference laboratory's normal range.

Baseline characteristics

Demographic characteristics collected were age, body mass index, and menopausal status. Cancer characteristics were size, tissue origin and differentiation, hormone and human epidermal growth factor receptor 2 status, and number of lymph node metastases. The tissue differentiation was graded by the Elston-Ellis modification of the Scarff–Bloom–Richardson [23]. A positive hormone status was an expression of either or both oestrogen or progesterone receptors on at least 10% of the cancer cells.

Quality of life and sample size

The EORTC QLQ-C30, version 3.0, contains one global QoL, five functional, and nine symptom scales. The 16-item breast cancer module contains four functional and four symptom scales. All scales result from adding their items and transforming the sum scores to range between 0 and 100 points. Each scale needs 50% valid items. Higher scores indicate better global and functional, but worse symptom-related QoL. The between-item-correlations, retest reliabilities, convergent and discriminant validities are well proven [24–26].

Based on phase II Gemcitabine studies [8], global QoL was the primary outcome. Secondary core outcomes were fatigue, emotional and physical functioning, and pain. Side effects of systemic therapy were the secondary breast module outcome. Global QoL includes two seven-point items rating overall health and QoL during the past week. *A* ≥ five-point change is clinically relevant [27]. With a planned study sample 3658 women [13], the power was sufficient for a 95%CI of less than ± one QoL point.

Randomisation and concealment

An external statistician performed the randomisation. The ratio of 1:1 was stratified by menopausal status, cancer differentiation, hormone and human epidermal growth factor receptor status, and number of lymph node metastases. The CRO informed the centres about the allocation by facsimile and the electronic case report form. The study was open-label; however, the CRO concealed the sequence.

Chemotherapy and further treatment

All cycles were body-surface adapted intravenous infusions. The FEC dose was respectively 500 mg/m^2 in 15 min, 100 mg/m^2 in 15 min, and 500 mg/m^2 in 60 min. The DG-dose was respectively 75 mg/m^2 in 60 min and 1000 mg/m^2 in 30 min. The D-dose was 100 mg/m^2 in 60 min. Dexamethasone, 2-mercaptoethanesulfonate-sodium, and serotonin-3-antagonists identically decreased the toxicity during the cycles in both groups [9]. After chemotherapy, all hormone receptor-positive women received 20 mg/d Tamoxifen orally until study end. Oral 1 mg/day Anastrozol replaced it in the event of contraindications. From the end of chemo to study end, all received 4 mg Zoledronate intravenous infusions quarterly. Radiotherapy followed chemotherapy in all women with breast-conserving surgery, cancer size > 3 cm, multifocal, multicentric or bilateral cancer, an N2 lymph node status, or with carcinomatous lymph- or haemangiosis [9].

Analysis

A blinded independent institution described and analysed the data with IBM SPSS Statistics 21. All were intention-to-treat, complete time-point analyses.

Multilevel linear models of repeated measurements estimated the mean QoL differences between FEC-DG versus FEC-D. T1 to t7 and their interaction with chemotherapy were random effects. The number of days between time-points was a covariate. The covariance structure between time-points was the one with the highest − 2 log-likelihood for global QoL. For the time-points overall and for the one with the largest difference, we computed the number of included women, the QoL differences, the CIs, and the *p* values. A line chart illustrated the prediction of global QoL by group and time-point.

To analyse informative participation—that is, whether the probability of reporting QoL is associated with higher QoL [18]—a generalised multilevel linear model estimated the odds ratio between FEC-DG versus FEC-D of reporting global QoL. Assuming binomial distribution of the repeated outcome, the logit function linked chemotherapy with it. The fixed effects, covariance structure, and numerical and

graphical presentation were as above. However, including the number of days between time-points would have excluded most non-participants.

Using Cox regression, the continuation of chemo- and bisphosphonate therapy until t7 was analysed. Sensitivity models on specific reasons for premature discontinuation (for reasons that occurred sufficiently often) treated discontinuation for reasons other than the reason currently being modelled as censored. The expected duration of 105 days of chemo plus 12 months of bisphosphonate therapy replaced the real duration if this information was missing. If women discontinued both therapies, the model accounted for the former.

Results

Baseline characteristics

The analysis included 3691 women (Fig. 1). Most had small hormone receptor-positive cancers and few lymph node metastases (Table 1).

QoL

Altogether, 3454 women returned at least one QoL questionnaire (Fig. 1). The last time point was t7 in 61% of the FEC-DG cases versus 60% with FEC-D, t6 in 7% versus 8%, t5 in 4% for both arms, t4 in 2% both arms, t3 in 9% versus 10%, t2 in 4% versus 3%, and t1 in 5% of both arms. The average delay between these and the other women is only 0.7 days.

The average global QoL varied between 51 and 69 points. The standard deviation varied between 19 and 21 points. Physical functioning scored best with little difference between groups. The dates of questionnaire completion varied most at t4. QoL, particularly global QoL and emotional functioning, was highest from t5 to t7 (Table 2). Apart from side effects of systemic therapy, t1 to t7 accounted for less than 10% of the variance. Pain varied the least over time. The between-time variance of side effects of systemic therapy was stronger with FEC-DG than with FEC-D (Table 3).

Therapy completion

Of the 3410 (92%) who completed chemotherapy (Fig. 1), 1619 (88%) started bisphosphonate therapy after FEC-DG and 1685 (90%) after FEC-D. Of the 281 (8%) discontinuing women, 65 (3%) began bisphosphonate therapy after FEC-DG and 50 (3%) after FEC-D. Severe toxicity was the main reason for discontinuing chemotherapy, namely in 4% with FEC-DG after an average of 77 days versus 3% with FEC-D after an average of 59 days. Most women stopping the bisphosphonate therapy chose to do this themselves (6% with FEC-DG vs. 5% with FEC-D; Table 4).

Effect of chemotherapy on QoL

Over all time points, the average global QoL was one point higher with FEC-DG than with FEC-D (95% CI: ± one point; $p=0.05$), which is a fifth of the minimal clinically relevant difference [24]. At t3, this difference reached its maximum of two points (95% CI: ± two points; $p=0.02$), again

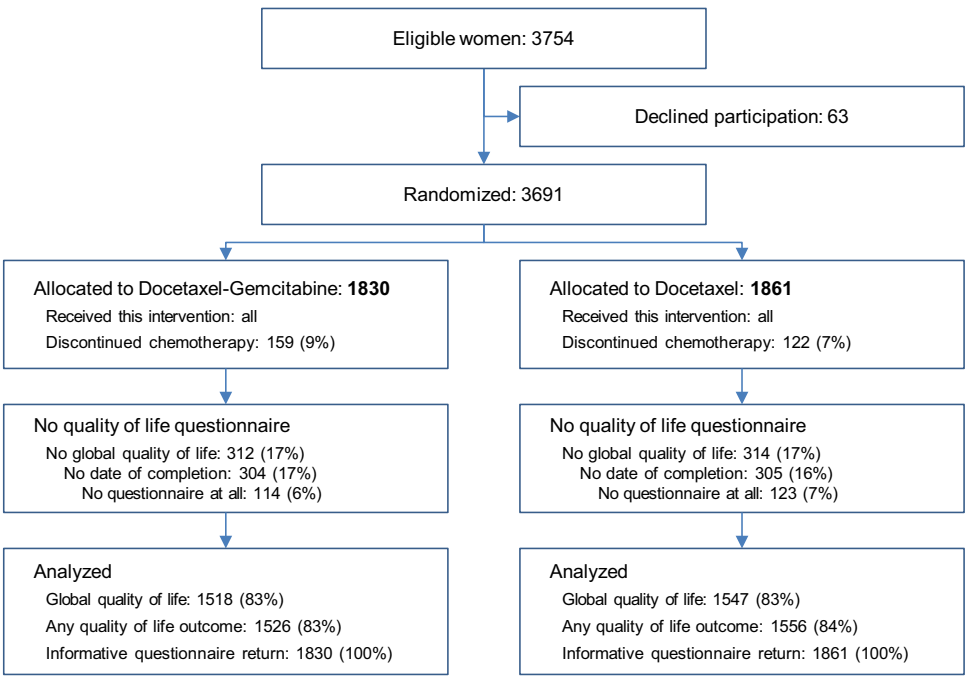

Fig. 1 Diagram of the participant flow

Table 1 Characteristics before chemotherapy

		Mean	Standard deviation	Minimum	Maximum
Age (years)		53	10	21	86
Body mass index		26	5	15	53
				N (% of non-missing)	
Postmenopausal				2149 (58)	
Tumour size	T1			1539 (42)	
	T2			1901 (52)	
	T3			194 (5)	
	T4			52 (1)	
	Missing			5	
Lymph node metastases	N0			1257 (34)	
	N1			1685 (46)	
	N2			507 (14)	
	N3			232 (6)	
	Missing			10	
Cancer tissue origin	Invasive ductal			3027 (82)	
	Invasive lobular			409 (11)	
	Other invasive epithelial			251 (7)	
	Missing			4	
Grading	G1			176 (5)	
	G2			1755 (47)	
	G3			1756 (48)	
	Missing			4	
Oestrogen and/or progesterone receptor-positive (3 missing)				2596 (70)	
Human epidermal growth factor receptor-2-positive (65 missing)				877 (24)	
Breast conserving surgery (1 missing)				2606 (71)	

favouring the FEC-DG group and again below the clinical relevance threshold. QoL decreased during chemotherapy and ended six points higher than before (Fig. 2).

While no QoL outcome differed by more than one point over all time points between FEC-DG versus FEC-D (95% CI always ± 1), t3 was always the time point with the largest difference, always favouring FEC-DG. This difference was clinically relevant for side effects of systemic therapy (Table 5). Women with FEC-DG reported significantly less pain and fatigue and a significantly better physical functioning at t3. However, as these differences were maximally four points, they were probably below clinical relevance.

Effect of chemotherapy on reporting global QoL

Over all time points, the odds of self-assessment of global QoL were 1.1 times higher with FEC-D than with FEC-DG (95% CI 1.0–1.1; $p = 0.23$). At t3, the ratio reached its maximum of 1.1 (95% CI 1.0–1.2; $p = 0.15$), again favouring FEC-D. That is, the questionnaire return proportion, which accounts for participation and correlates with higher QoL [18], was the same for both regimens. With both treatments, the probability to report QoL decreased by 25% by t4 and then was stable (Fig. 3).

Effect of chemotherapy on continuation of therapy

Table 6 shows that the hazard of continuing therapy was 1.2 times higher with FEC-D than with FEC-DG (95% CI 1.0–1.4; $p = 0.03$). That is, women in the former group were slightly more likely to continue.

Discussion

After prior anthracycline treatment, DG is as beneficial as D for the QoL course of women with high-risk early breast cancer, as the one-point difference was below clinical relevance and the participation was the same. With both regimens, the long-term increase in QoL is clinically relevant, as the improvement seen from t1 to t5 and lasting until t7 was six points ($p < 0.001$) and good participation correlates with good QoL [18]. More precisely, the favourable effects of both chemotherapies on QoL are probably more durable

Table 2 Quality of life by chemotherapy and time-point

Scales in mean points ± standard deviation	Before, during, at the end, and quarterly after (Q.) chemotherapy						
	Before (t1)	During (t2)	End (t3)	1st Q. (t4)	2nd Q. (t5)	3rd Q. (t6)	4th Q. (t7)
Days from t1 (*N*)							
Number of questionnaires returned	3690	2266	2271	1904	1891	1918	1943
Docetaxel-Gemcitabine	0	70 ± 32	149 ± 43	246 ± 77	328 ± 54	416 ± 55	506 ± 61
Docetaxel	0	69 ± 32	139 ± 39	235 ± 57	316 ± 52	404 ± 52	491 ± 57
Global quality of life (*N*)							
Number of questionnaires returned	3005	2699	2680	2221	2156	2166	2213
Docetaxel–Gemcitabine	62 ± 21	56 ± 20	53 ± 21	65 ± 20	68 ± 19	68 ± 19	20
Docetaxel	61 ± 21	55 ± 19	51 ± 21	63 ± 19	67 ± 20	67 ± 20	66 ± 20
Fatigue (*N*)							
Number of questionnaires returned	3061	2728	2717	2247	2170	2185	2229
Docetaxel–Gemcitabine	28 ± 23	45 ± 24	49 ± 26	35 ± 24	32 ± 23	31 ± 23	23
Docetaxel	29 ± 23	46 ± 25	52 ± 27	37 ± 25	33 ± 25	33 ± 24	33 ± 24
Emotional functioning (*N*)							
Number of questionnaires returned	3033	2716	2702	2229	2162	2176	2219
Docetaxel–Gemcitabine	62 ± 24	63 ± 24	61 ± 25	67 ± 24	68 ± 24	69 ± 24	24
Docetaxel	62 ± 24	63 ± 25	60 ± 25	67 ± 25	68 ± 25	69 ± 24	68 ± 24
Physical functioning (*N*)							
Number of questionnaires returned	3064	2726	2721	2248	2170	2190	2227
Docetaxel–Gemcitabine	86 ± 16	76 ± 19	72 ± 21	81 ± 18	84 ± 17	84 ± 17	17
Docetaxel	86 ± 16	75 ± 19	69 ± 22	80 ± 18	83 ± 17	83 ± 17	83 ± 17
Pain (*N*)							
Number of questionnaires returned	3070	2732	2722	2247	2171	2191	2231
Docetaxel–Gemcitabine	28 ± 27	24 ± 27	28 ± 29	27 ± 28	27 ± 28	26 ± 27	27
Docetaxel	29 ± 27	25 ± 27	32 ± 30	29 ± 29	27 ± 27	27 ± 27	27 ± 28
Therapy side effects (*N*)							
Number of questionnaires returned	2984	2708	2686	2209	2145	2171	2199
Docetaxel–Gemcitabine	14 ± 15	48 ± 19	43 ± 21	25 ± 18	22 ± 16	22 ± 16	21 ± 16
Docetaxel	14 ± 14	48 ± 19	50 ± 21	27 ± 18	22 ± 16	22 ± 15	22 ± 15

Table 3 Variance of quality of life between women and time-points by chemotherapy

Scales in points	Docetaxel–Gemcitabine (*N* = 1830)		Docetaxel (*N* = 1861)	
	Between patient variance (%)	Between time variance (%)	Between patient variance (%)	Between time variance (%)
Global quality of life	405 (91)	42 (9)	410 (91)	41 (9)
Fatigue	577 (92)	68 (8)	618 (89)	73 (11)
Emotional functioning	594 (98)	11 (2)	612 (98)	13 (2)
Physical functioning	318 (92)	29 (8)	330 (90)	38 (10)
Pain	763 (100)	2 (0)	783 (99)	4 (1)
Therapy side effects	303 (63)	180 (27)	290 (58)	209 (42)

than their short-term adverse influences. However, additional treatment with zoledronate applied equally to both groups might also contribute to the long-term increase of QoL. Zoledronate may contribute by preventing disease recurrences or by promoting faster bone recovery from chemotherapy [28]. A perhaps even simpler explanation is that the cancer diagnosis and the need of surgery diminish QoL. At long term, the recovery from chemotherapy and the hope that this therapy removed the last remnants of the cancer probably restore QoL to a level similar to that before diagnosis.

The secondary outcomes support the conclusion of the primary outcome. In line with prior findings [20, 21], the superiority of DG in four of five scales at t3 is very short.

Table 4 Reason for and time to discontinuation from therapy

Discontinuation counts (% of *N*) and mean days from t1 ± standard deviation	Chemotherapy (t1 to t3)				Bisphosphonate therapy (t4 to t7)			
	Docetaxel–Gemcitabine (1830 women)		Docetaxel (1861 women)		Docetaxel–Gemcitabine (1830 women)		Docetaxel (1861 women)	
	Count (%)	Mean ± SD	Count (%)	Mean ± SD	Count (%)	Mean ± SD	Count (%)	Mean ± SD
All reasons	159 (9)	71 ± 49	122 (7)	59 ± 41	319 (17)	185 ± 127	286 (15)	171 ± 127
Participant's desire	56 (3)	80 ± 70	39 (2)	65 ± 44	118 (6)	190 ± 127	99 (5)	154 ± 113
Severe toxicity	67 (4)	77 ± 26	55 (3)	59 ± 34	46 (2)	163 ± 125	52 (3)	138 ± 130
Cancer progression	4 (0)	49 ± 8	3 (0)	10 ± 15	43 (2)	324 ± 104	32 (2)	308 ± 139
Death	2 (0)	–	3 (0)	44 ± 1	10 (0)	197 ± 113	11 (1)	223 ± 126
Lost to follow-up	4 (0)	50 ± 20	2 (0)	1 ± –	17 (1)	120 ± 77	7 (0)	249 ± 237
Other reasons	26 (1)	46 ± 36	20 (1)	61 ± 55	85 (5)	144 ± 106	85 (5)	151 ± 102

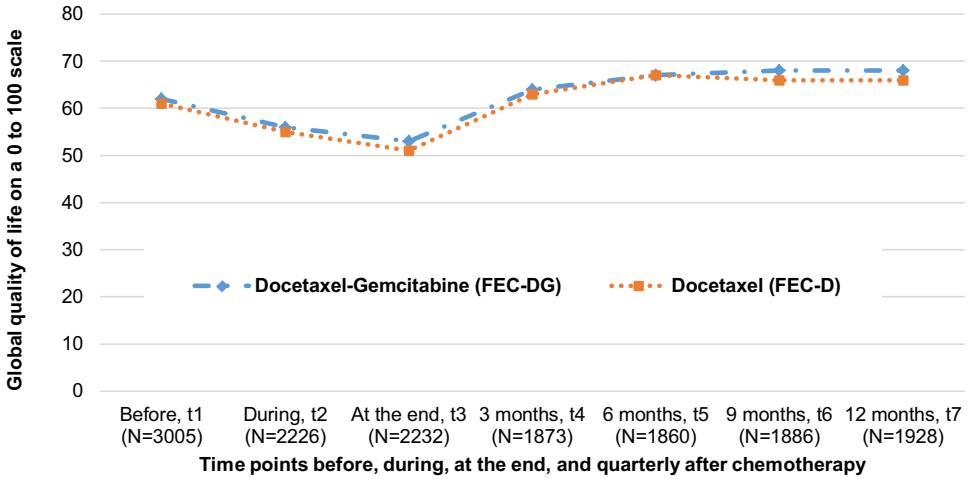

Fig. 2 General linear model of average global quality of life by chemotherapy and time-point

Table 5 General linear models of secondary outcomes by chemotherapy and time-point (Docetaxel–Gemcitabine minus Docetaxel)

0 to 100 scales in points	Included	Mean difference	95% confidence	*p* value
Fatigue				
Over all time-points	3075	−1	±1	0.09
At largest difference (end of chemotherapy, t3)	2257	−2	±2	0.02
Emotional functioning				
Over all time points	3073	0	±1	0.29
At largest difference (end of chemotherapy, t3)	2248	1	±2	0.25
Physical functioning				
Over all time points	3077	1	±1	0.06
At largest difference (end of chemotherapy, t3)	2261	3	±1	< 0.001
Pain				
Over all time points	3079	−1	±1	0.11
At largest difference (end of chemotherapy, t3)	2261	−4	±2	0.001
Therapy side effects				
Over all time points	3066	−1	±1	0.004
At largest difference (end of chemotherapy, t3)	2230	−6	±1	< 0.001

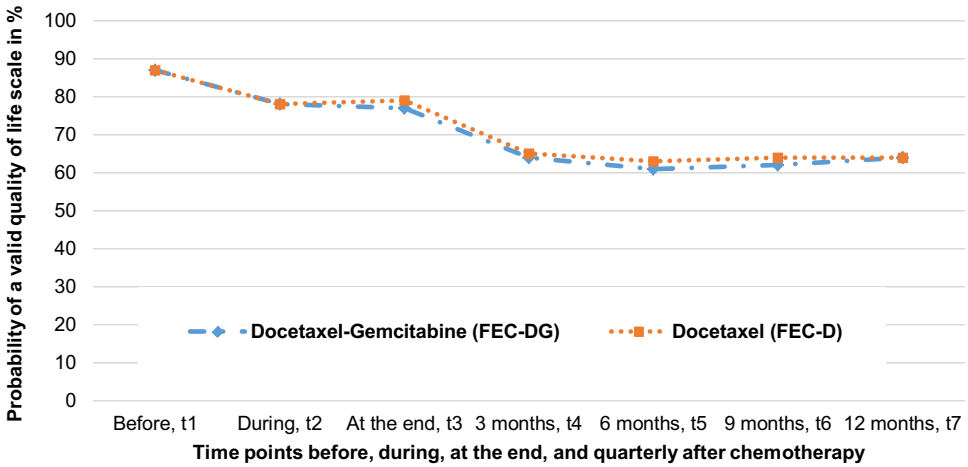

Fig. 3 Logistic linear model of the average probability of self-assessment of global health by chemotherapy and time-point

Table 6 Continuation of chemo- and bisphosphonate therapy by chemotherapy (Docetaxel–Gemcitabine divided by Docetaxel)

	Continuers/included	Hazard ratio	95% confidence	*p* value
Overall continuation	2330/2807	0.8	0.7 to 1.0	0.03
Patients' desire to continue	2736/2807	0.7	0.4 to 1.1	0.16
Survival from toxicity	2715/2807	0.8	0.5 to 1.2	0.82
Progression-free survival	2803/2807	1.0	0.1 to 7.0	0.98

It is clinically relevant for therapeutic side effects (six points, $p < 0.001$) and perhaps relevant for pain (four points, $p = 0.001$) and physical functioning (three points, $p < 0.001$). A pain increase needs three points for clinical relevance, but a decrease needs five. The circumstances are similar for physical functioning [27].

A strength of this study is that four independent institutions collected and analysed representative nationwide data with regular quality checks during the study and a thorough final validation after a long-term follow-up was carried out. The separate responsibilities for randomisation, allocation concealment, data management, data collection, and blinded analysis minimised influences of potential conflicts of interest. Each institution counter-checked the information transmitted by the others.

We were the first to compare the one-year evolution of QoL between a taxane-Gemcitabine combination and a single-agent taxane after prior anthracycline treatment [10–12, 15]. The improvement that we found with both regiments was stronger and more persistent than in studies comparing other treatments [20–22]. This could be due to the superiority of anthracycline combinations followed by taxanes or to our non-chemotherapeutic modalities, such as bisphosphonates. Future clinical trials may address these important hypotheses.

Adding to the disagreement of prior studies regarding recurrence-free survival [10–12, 15], in the SUCCESS-A trial we found that it was equal in the FEC-D and FEC-DG arms [13]. We also found that more haematologic toxicities, a need for granulocyte colony-stimulating factor, and dose reductions with FEC-DG [9] disagree with the better QoL related to side effects of therapy at t3 with this treatment. Perhaps neuropathy, arthralgia, and bone pain, which are more frequent with FEC-D [9], influence QoL more strongly than the former.

Taken together, we favour taxane therapies without Gemcitabine after prior anthracycline treatment because of equal survival [10–13, 15], fewer hematologic toxicities and need for adaptations, [9] and equal QoL. Thereby, we challenge prior recommendations favouring combination therapies [14, 15].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Written informed consent was obtained from all participants.

Research involving human participants and/or animals Led by the ethical board of the Ludwig-Maximilian-University of Munich, 37 local boards approvedall procedures performed in this study in accordance

with the ethical standards of 1964 Helsinkideclaration and its later amendments as well as the current laws of Germany.

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