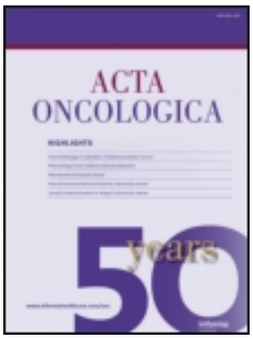

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ORIGINAL ARTICLE

Tailored chemotherapy doses based on toxicity in breast cancer result in similar quality of life values, irrespective of given dose levels

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Abstract

Background. From March 1994 to March 1998, breast cancer patients (an estimated relapse risk with 70% or more within five years with standard therapy) were randomised to treatment with tailored fluorouracil, epirubicin, and cyclophosphamide (FEC) therapy or FEC followed by marrow-supported high dose therapy in the Scandinavian Breast Group 9401 study. The aim of the present paper was to investigate differences in toxicity and eight health-related quality of life (HRQoL) variables (physical functioning, role functioning, emotional functioning, social functioning, cognitive functioning, fatigue, nausea-vomiting, and global quality of life) between women in the six dose steps used in the tailored and granulocyte colony stimulating factor supported FEC-arm at the assessment point 16 weeks after random assignment to treatment. *Methods.* The European Organization and Treatment of Cancer Quality of Life Questionnaire EORTC QLQ-C30 were mailed to the patients. *Results.* A total of 157 (87%) in the tailored FEC-group responded to the questionnaire within the time frame 16 weeks after inclusion in the study. Overall, toxicity was low, reaching grade 1-2 also in the higher dose steps. There were no overall differences between the dose steps on any of the tested HRQoL variables. Patients at dose step 4 scored statistically significantly higher on physical functioning than patients at dose step 1 ($p = 0.022$) and compared to those at dose step 2 ($p = 0.014$). Patients at dose steps –2 and –1 (combined to one group) reported statistically significantly higher mean scores on cognitive functioning than patients at dose step 1 ($p = 0.022$). *Conclusion.* Patients who received higher doses, based on the tailored dosing strategy, did not seem to have worse HRQoL than those who had lower doses.

In a Scandinavian study (the SBG-9401 study) 525 high-risk breast cancer patients were randomly assigned to two different adjuvant regimens [1]. Nine courses of tailored and granulocyte colony-stimulating factor (G-CSF)-supported FEC-therapy (the tailored FEC group) was compared with induction standard FEC-therapy for three courses (further courses if required for logistic reasons) followed by high-dose chemotherapy with cyclophosphamide, thiotepa, and carboplatin (CTCb) supported by PBSCs (the CTCb group). In an update of the study after a median follow-up of 60.8 months there were fewer breast cancer relapses in the tailored FEC group compared with the CTCb arm, 104 versus 139 ($p = 0.046$), but no difference in overall survival [2]. There was an increased incidence of AML/MDS ($n = 10$) in the tailored FEC arm, very likely due to the very high cumulative doses of epirubicin and cyclophosphamide, respectively [2].

Evaluation of health related quality of life (HRQoL) was a secondary endpoint in the SBG-9401 study [3]. Finland, Norway and Sweden participated in the HRQoL-study. The results revealed that both treatments had a negative influence on HRQoL during the treatment period, especially at the assessment point 16 weeks after random assignment to treatment. One year after inclusion in the study, however, the levels of HRQoL on most variables were comparable with those found at inclusion in the study. The results have been described in detail elsewhere [3].

Dosage of conventional chemotherapy is frequently based on body surface area (BSA) adapted calculations of chemotherapy doses. Despite this BSA based

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adaptation, this will result in marked inter-patient variations in pharmacokinetics [4]. Pharmacokinetic variations for the standard F600E60C600 regimen have also been observed [5]. Individual variation in pharmacokinetics will likely contribute to over-dosage of chemotherapy resulting in toxicity as well as under-dosage, potentially leading to an increased risk of therapy failure.

An increased use of dose-escalated and/or dose-dense chemotherapy regimens raises questions about how about how women treated at various dose levels experience HRQoL during treatment. Decline in HRQoL during therapy has been shown to predict early treatment discontinuation even after accounting for age and chemotherapy-related side effects [6]. Thus, it is important to evaluate HRQoL in the various dose-steps. If the tailored dose strategy results in worse HRQoL in the higher dose steps, these women may discontinue their treatment and thus jeopardise the effect of treatment and the tailored strategy.

The present paper aims at evaluating differences between women in the six dose steps used in the tailored and G-CSF supported FEC-arm with respect to toxicity and eight HRQoL variables at the assessment point 16 weeks after random assignment to treatment. The hypothesis was that women receiving the higher dose steps would report worse HRQoL than those in the lower steps.

Patients and methods

Patients

Patients with histologically confirmed breast cancer, < 60 years of age, with an estimated 5-year relapse-free survival of $\leq 30\%$, and a life expectancy exceeding three months were included in the SBG-9401 study [1,2]. Inclusion and exclusion criteria, as well as inclusion in the HRQoL study has been outlined in detail elsewhere [1,3]. Patients were required to have eight or more (in Stockholm six or more) involved axillary lymph nodes or five or more positive lymph nodes, negative hormone receptors, and either nuclear anaplasia grade 2-3 (or an equivalent high-grade criterion) or a high S-phase fraction. Breast conserving surgery or mastectomy was required before randomisation. Patients were required to have normal bone marrow morphology, normal chest radiograph and adequate cardiac, liver and renal function. Patients with distant metastasis or previous cancer (excluding cervical carcinoma *in situ*, basal cell carcinoma or contralateral breast cancer) were ineligible. Other reasons for ineligibility included inadequate psychological function, serious disease co-morbidity or uncontrolled infection, and pregnancy or lactation.

In the tailored and dose-escalated FEC-group chemotherapy was given in escalated or diminished doses based on haematologic toxicity, i.e. to the reaction in the patients white blood cell count. All patients started at dose step 1. Thus women who did not reach a predefined reduction in their leukocyte count got a higher dose of chemotherapy. Consequently, women with a large reduction of their leukocyte count received a lowered dose. After each course 1-8, the haematological toxicities were determined day 8, 11/12, 15 and 22 (day 1 next course) and the next course was delivered based on the recorded toxicities. The tailored FEC regimen is described in Table I.

The patients received written and oral information about the HRQoL study and written informed consent was obtained. The HRQoL amendment was approved by the ethics committees in all three participating countries.

Procedure

Data on HRQoL were collected by mailed questionnaires, sent to the patients with a prepaid envelope from the three coordinating centres of the HRQoL part of the SBG-9401 study. One reminder was sent after two weeks in case of no reply. After confirmation by the physician who included the patient in the SBG-9401 study, a second reminder was sent. HRQoL was assessed at eight points during the first year from random assignment to treatment. The assessment points and data collection procedure are outlined in detail elsewhere [3].

The present paper includes data collected at the *16-weeks assessment point for the patients in the tailored FEC-group* responding to questionnaires within the time frame set. At this assessment point, the patients in the tailored FEC-group were expected to be in the middle of their chemotherapy treatment and to experience maximum of side-effects. A further support for choosing the 16-weeks assessment point was that the lowest mean scores on HRQoL the tailored FEC-group were obtained at that time [3]. Data from the

Table I. Description of the tailored FEC doses.

Step	Fluorouracil dose (mg/m²)	Epirubicin dose (mg/m²)	Cyclofosfamide dose (mg/m²)	Mesna dose (mg/m²)*
−2	300	38	450	—
−1	600	60	600	—
+1	600	75	900	—
+2	600	90	1200	720
+3	600	105	1500	900
+4	600	120	1800	1080

*Total dose given.

tailored FEC group collected at this point was therefore used for the examination of differences between the six dose steps.

Toxicity data were collected from CRF's corresponding to the 16-weeks assessment point, within the time frame of within two weeks after treatment.

Instruments

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) is a HRQoL questionnaire for the measurement of quality of life in cancer patients in clinical trials, developed by the European Organization for Research and Treatment of Cancer (EORTC Quality of Life Study Group) [7]. In the present study, EORTC QLQ-C30+3 was used. The EORTC QLQ C-30 (+3) is the second generation of the core questionnaire and was the version available at the start of the present study. It consists of 33 items constituting five functional scales (physical, role, cognitive, emotional and social); nine symptom scales (fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties); and one global health and quality of life scale. The respondents are asked to indicate for each item the extent to which he/she has experienced the problem during the past week on a four-point scale from 1 ("Not at all") to 4 ("Very much"). Global quality of life items are scored on a 1 ("Very poor") to 7 ("Excellent") point scale. A number of single item scales are also included. The validity and reliability of the Swedish version of the EORTC QLQ C-36 was established in a study of patients with lung cancer [8], and in a study of patients with generalised cutaneous malignant melanoma [9].

The following variables were chosen for analysis of differences between the dose steps: physical functioning, role functioning, emotional functioning, social functioning, cognitive functioning, fatigue, nausea/vomiting, and global quality of life. The variables selected were those where the patients in the FEC-group reported the highest levels of problems in the previous paper [3]. In addition, the variable nausea/vomiting was selected since these problems were expected to be related to the chemotherapy doses received.

Statistical methods

A time frame for inclusion of questionnaires was decided in order to catch problems related to the treatment. Included questionnaires at the assessment 16 weeks after random assignment were responded to within two weeks *after* the tailored FEC course.

Mean scales and item scores were transformed to a 0 to 100 scale according to the EORTC scoring manual [10]. No substitutions for missing items were made. Dose step –2 and –1 were combined due to low number of patients in dose step –2, Thus, HRQoL in the five dose steps before random assignment and 16 weeks after were compared by ANOVA-factorial design. Post hoc tests were performed by Fischer PLSD.

Results

A total of 446 women of 525 randomised, were eligible for the HRQoL part of the SBG-9401 study. The HRQoL-study included 408 patients (91% of eligible HRQoL patients). A total of 197 patients (48%) were randomly assigned to the tailored FEC group. At the 16-weeks assessment 180 patients (91% of included patients) in the tailored FEC-group responded to the questionnaire. Out of them, 157 of the patients (87%, 80% of included patients) responded to the questionnaire within the time frame and were included in the analysis. Mean age was 48 years (range 25 to 62 years).

Dose steps according to number of courses 16 weeks after random assignment are presented in Table II. The majority of the patients, 69% (n = 125) received six courses of tailored FEC before the HRQoL assessment.

Toxicity at the different dose steps is shown in Table III, as evaluated after each course by the treating physician. Overall, toxicity was low, reaching grade 1-2 also in the higher dose steps. Grade 3 or 4 toxicity was most common in the higher dose steps, where infections, myalgia and bone pain often were reported.

Comparison of HRQoL between the dose steps

Mean values and standard deviations in the five dose steps 16 weeks after random assignment are presented in Table IV. There were no overall differences between the dose steps on any of the tested HRQoL variables. Patients at dose step 4 scored statistically

Table II. Dose step at the 16 weeks assessment according to number of courses of FEC.

	Number of courses of FEC									
Dose step	1n	2n	3n	4n	5n	6n	7n	8n	9n	Total n (%)
–2						5	1			6 (3)
–1					4	12	3		1	20 (11)
1		1		1	2	19	5			28 (16)
2				2	4	36	4			46 (26)
3				1	9	28	7	2		47 (26)
4					5	25	3			33 (18)
Total		1		4	24	125	23	2	1	180 (100)

Table III. Numbers of patients (%)[1] with toxicity according to the five dose steps[2].

Toxicity 157 patients	Dose step –1,–2 24 patients[3] n (%)				Dose step 1 20 patients n (%)				Dose step 2 40 patients[4] n (%)				Dose step 3 43 patients[5] n (%)				Dose step 4 30 patients[6]			
Toxicity grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Haematological	1 (4)	–	–	–	1 (5)	–	–	–	–	–	–	–	–	–	–	–	1 (4)	–	–	–
Nausea	12 (50)	2 (8)	–	–	11 (55)	1 (5)	1 (5)	–	18 (64)	4 (14)	–	–	14 (31)	9 (20)	–	–	18 (72)	2 (8)	–	–
Stomach pain	7 (30)	3 (13)	–	–	3 (15)	2 (10)	–	–	4 (14)	3 (11)	–	–	10 (22)	3 (7)	–	–	2 (8)	–	–	1 (4)
Alopecia	1 (4)	23 (96)	–	–	–	19 (95)	–	–	–	29 (100)	–	–	–	35 (92)	–	1 (3)	–	24 (96)	–	–
Bone pain	6 (25)	3 (12)	–	–	6 (30)	4 (20)	–	–	5 (18)	4 (14)	–	–	9 (28)	2 (4)	2 (4)	–	3 (12)	3 (12)	–	–
Myalgia	4 (17)	2 (8)	1 (4)	–	5 (25)	2 (10)	–	–	8 (29)	2 (7)	–	–	7 (20)	3 (7)	3 (7)	.	1 (4)	1 (4)	–	–
Diarrhoea	–	2 (8)	1 (4)	–	2 (10)	–	3 (15)	–	4 (14)	1 (4)	–	–	5 (11)	2 (4)	–	–	10 (40)	1(4)	–	–
Infections	2 (8)	–	1 (4)	–	2 (10)	2 (10)	1 (5)	–	5 (17)	2 (7)	1 (3)	–	3 (7)	3 (7)	–	–	1 (4)	1 (4)	–	2 (8)
Anorexia	5 (21)	–	–	–	5 (25)	1 (5)	1 (5)	–	6 (22)	3 (11)	1 (4)	–	13 (29)	5(11)	–	–	17 (68)	5 (20)	–	–
Vomiting	5 (21)	2 (8)	–	1(4)	2 (10)	–	–	1 (5)	4 (14)	4 (14)	1 (7)	1 (7)	7 (16)	4 (9)	1 (2)	–	10 (40)	2 (8)	–	–

[1]Dose step −2 and −1 were combined.
[2]Percentages based on number of patients with data.
[3]Number of missing data for dose step -2,-1: Stomach pain = 1.
[4]Number of missing data for dose step 2: Anorexia = 13; Diarrhoea, Nausea, Vomiting, Stomach pain, Haematologic, Bone pain, Myalgia = 12; Infections, Alopecia = 11.
[5]Number of missing data for dose step 3: Anorexia, Diarrhoea, Nausea, Vomiting, Stomach pain, Infections, Haematologic, Bone pain, Myalgia = 8; Alopecia = 6.
[6]Number of missing data for dose step 4: Anorexia, Diarrhoea, Nausea, Vomiting, Stomach pain, Infections, Alopecia, Haematologic, Bone pain, Myalgia = 5.

significantly higher on physical functioning than patients at dose step 1 ($p = 0.022$) and compared to those at dose step 2 ($p = 0.014$). Patients at dose steps –2 and –1 (combined to one group) reported statistically significantly higher mean scores on cognitive functioning than patients at dose step 1 ($p = 0.022$). No other differences were found by Fisher PLSD post hoc tests. The patients at dose step 1 had the lowest nominal mean scores on five of the eight tested variables.

In order to investigate initial differences between women in the various dose steps (the five dose steps at the 16-weeks assessment) HRQoL data from the assessment at random assignment was analysed. No statistically significant HRQoL differences were found between the groups at the assessment point at random assignment.

Discussion

Tailored chemotherapy is based on the concept that every patient receives doses that is individualised according to toxicity. This concept is supported by six retrospective analyses, demonstrating a worse outcome for patients receiving adjuvant chemotherapy without toxicity [11–16], thus implying a relationship between normal cell- and cancer cell reactivity to cytotoxic compounds. One negative study has, however, been reported [17]. Although the data was collected between 1994 and 1998, the analyses are new and highly relevant today. The tailored strategy is still used today in one therapy arm with epirubicin-cyclophosphamide followed by doxetaxel as part of an ongoing randomised and prospective study, the PANTHER (PaN-european Tailored CHemoTHeRapy) study, in the adjuvant setting; joint project between the Swedish Breast Cancer Group, the Austrian Breast and Colorectal cancer study Group and the German Breast Cancer group. Patients receiving different targeted drugs may have a better effect if they experience toxicities, further supporting that tailoring is not reached by standard dosage modifications [18]. Based on this notion it was considered important to study the associations between dose step and HRQoL.

High dose chemotherapy has been reported to affect HRQoL negatively to a higher extent than conventional chemotherapy doses shortly after treatment, but these differences were negligible one year later [3,19]. In the SBG-9401 study, as in other studies, low correlations were found between toxicity and HRQoL [3,20]. It was therefore considered important to investigate the impact on HRQoL of the tailored doses, given at each course except for the first, to equivalent haematological toxicity for each patient [1]. HRQoL is subjective in that it is the patients'

Table IV. Mean values (SD) on EORTC QLQ-30 variables according to the five dose steps*.

	Dose steps				
HRQOLvariables	–1 & –2*n = 24 mean (SD)	**1** n = 20 mean (SD)	**2** n = 40 mean (SD)	**3** n = 43 mean (SD)	**4** n = 30 mean (SD)
PhysicalFunctioning[1]	66.4 (27.5)	63.1 (23.1)	64.0 (25.1)	69.1 (26.6)	78.7 (24.7)
RoleFunctioning[1]	55.1 (33.3)	44.2 (30.2)	55.2 (31.9)	53.6 (32.2)	55.6 (33.5)
EmotionalFunctioning[1]	67.0 (24.9)	63.6 (27.9)	72.3 (22.4)	72.0 (21.2)	62.1 (23.6)
Cognitive Functioning[1]	88.0 (15.6)	73.5 (26.7)	78.2 (24.6)	81.2 (23.2)	79.3 (20.4)
SocialFunctioning[1]	63.3 (30.8)	53.6 (29.2)	56.7 (31.7)	56.2 (27.7)	60.1 (28.2)
Global Quality of Life[1]	49.4 (24.9)	42.0 (23.0)	50.9 (24.2)	50.7 (19.5)	46.2 (24.2)
Fatigue[2]	52.6 (27.9)	54.3 (26.9)	58.0 (27.7)	54.1 (24.8)	54.9 (28.2)
Nausea/Vomiting[2]	16.7 (17.6)	19.0 (23.9)	19.6 (30.2)	23.7 (25.7)	22.2 (26.6)

*Dose steps –1 and –2 were combined.
[1]Higher mean values indicate better functioning.
[2]Higher mean values indicate more problems.

own reported perceptions in contrast to toxicity, which is the assessment made by professionals. In the present study, no differences were found in HRQoL between the various dose steps. Our findings further support the individualised and tailored dosage strategy in that this procedure does not seems to affect quality of life negatively among those in the higher dose steps. Patients who received higher doses, based on our tailored dosing strategy, did not seem to have worse HRQoL than those who had lower doses. This is surprising, while patients could be expected to have worse HRQoL when they receive higher doses or higher dose intensity [21]. The risk that patients at higher dose steps discontinue treatment due to impairment of quality of life seems therefore equivalent to those at lower dose steps.

Analyses of differences in HRQoL at the assessment point at random assignment were performed between the dose steps in order to exclude the possibility of differences before the start of treatment. However, we found no differences, indicating that the patients were similar at that assessment point, at least when it comes to HRQoL. Obviously, however, there are differences between the patients in the various dose steps in terms of metabolism of chemotherapy. There might also be other differences, but the focus of this paper was to explore if the tailored dose strategy resulted in differences in HRQoL, given no differences found in HRQoL at random assignment. A patients' HRQoL is, of course, also affected by other factors in the patients' life.

At the 16-weeks assessment, patients at dose step 1 seemed to have somewhat lower mean scores on five of the eight tested variables, statistically significant only with respect to physical functioning, compared with patients at dose step 4, and worse cognitive functioning compared with patients at dose steps –1 and –2. Decreased cognitive functioning following adjuvant chemotherapy in breast cancer is being debated [22], but evidence is mounting that adjuvant chemotherapy for breast cancer may result in longstanding cognitive impairment [23]. Thus, an interpretation of our findings of a statistically lower level of cognitive disturbance in dose steps –1 and –2 as compared to dose step1 is that the patients at dose step 1 had received higher doses of FEC. Consequently, those receiving even higher doses should report more cognitive disturbances, but this was not seen in our study, further supporting that the patients in our study received individually optimal doses.

Another somewhat surprising finding was that the patients at dose step 4 had a statistically significantly higher mean score on physical functioning than those treated at step 1 and 2. Taken together, our findings indicate that the tailored dosage could be further refined, while the patients at step 1 tended to experience more subjective toxicity.

As have been reported earlier, most HRQoL variables decreased statistically significantly from random assignment to the 16 weeks assessments, with the exception of emotional functioning which improved [3]. Thus, the questionnaire seems to be sensitive enough to reveal differences in HRQoL between the dose steps.

It could be argued that the lack of differences found between the dose steps could be due to a floor effect in that HRQoL is at its worse at the 16-week assessment. Theoretically, however, the mean scores for all variables could have been even further impaired [24]. Another explanation of the lack of statistically significant differences could be the small number of patients at the various dose steps. The number of patients at each dose step exceeded, however, 25 for all groups except for dose step –1 and dose step –2, which therefore were combined to one group. No pattern of HRQoL corresponding to the increased doses appeared, thus it is unlikely that our results are due to low number of patients. As fluctuations in quality of life could be expected during a therapy cycle, thus confounding differences in experienced

HRQoL, a time frame of within two weeks from receiving FEC was decided upon for completion of questionnaires. The number of included patients was therefore further restricted.

Conclusion

Similar HRQoL among women at the various dose steps were found at a point in time where the majority had received more than five or more courses of individually tailored doses of FEC. This indicates that individually tailored higher doses of FEC do not result in poorer HRQoL than individually tailored lower doses. Our results in the SBG 9401 study will also be prospectively tested in another randomised study comparing a tailored and dose dense epirubicin-cyclophospamdide-docetaxel strategy with a three-weekly regimen in collaboration with the Austrian (ABCSG) - and German Breast Cancer (GBG) groups (PANTHER study). This study also contains HRQOL evaluation.

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

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