Chapter 2

Prospective study of long-term impact of adjuvant high-dose and conventional-dose chemotherapy on health-related quality of life

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ABSTRACT

Purpose

To evaluate and compare Health Related Quality of Life (HRQoL) after conventional- and high-dose adjuvant chemotherapy in patients with high-risk breast cancer.

Patients and methods

Patients were randomized between a conventional and high-dose chemotherapy regimen; both followed by radiotherapy and tamoxifen. HRQoL was evaluated until disease progression, using the Short-Form (SF-36), Visual Analogue Scale (VAS) and Rotterdam Symptom Checklist (RSCL) and assessed every 6 months for 5 years following randomization. For the SF-36 data from healthy Dutch women with the same age distribution served as reference value.

Results

804 patients (405 conventional-dose, 399 high-dose chemotherapy) were included. Median follow-up was 57 months. Directly after high-dose chemotherapy HRQoL decreased more compared to conventional chemotherapy for all SF-36 subscales. After 1 year the reference value of healthy women was reached in both groups. Small differences were observed between the two groups in the subscale role-physical and role-emotional, but 1 year after treatment these differences were minor and not clinically relevant. During follow-up, patients with a lower educational level and many complaints before chemotherapy experienced a worse HRQoL.

Conclusion

Shortly after high-dose chemotherapy, HRQoL was more affected than after conventional-dose chemotherapy. One year after randomization differences were negligible. Identifying patients who have a higher chance of persistent impaired quality of life after treatment, in the present study those with a lower educational level and many complaints before chemotherapy, is important and may open the way for better patient-tailored prevention strategies.

INTRODUCTION

Adjuvant therapy is administered increasingly to women with breast cancer, resulting in delayed disease recurrence and improved survival. Because of the dismal prognosis of patients with extensive axillary nodal involvement, over the last 10 years a variety of new treatment regimens has been tested. These include adjuvant dose-dense, as well as high-dose chemotherapy with hematopoietic stem-cell reinfusion. A number of randomized studies have been performed.[1] A recent meta-analysis shows a significant benefit in event-free survival for the high-dose group at 3 and 4 years. Overall survival rates were not significantly different, but most studies are still immature.[1]

Relatively little is known about the long-term effects of adjuvant therapy on patients' well-being. Long-term data concerning health-related quality of life (HRQoL) in breast cancer patients following chemotherapy, particularly after high-dose chemotherapy, are limited.[2-10] Most studies used cross-sectional designs with small and heterogeneous patient samples, and relatively short follow-up.

In a Dutch randomized, multi-center study, high-dose chemotherapy improved relapse-free survival of stage II and III breast cancer patients with 10 or more positive axillary lymph nodes.[11] An update showed a trend for a better relapse-free survival in the high-dose arm. For the 621 patients with *HER2/neu*-negative disease there was a relapse-free survival and survival benefit of high-dose therapy.[12] HRQoL was included as a secondary endpoint. In this paper we report the longitudinal HRQoL results of this trial.

PATIENTS AND METHODS

Patients

Patients with stage II-III breast cancer were eligible for the trial if they had ≥ 4 positive axillary lymph nodes, an ECOG-Zubrod performance status of 0 or 1, and if they were younger than 56 years. Prior to randomization, patients were stratified according to age (< 50 years versus ≥ 50 years), menopausal status (pre- or postmenopausal), number of lymph node metastases (4-9 or ≥ 10) and tumor size (pT1, pT2, or pT3).[11,12]

Treatment regimens

Patients received 5 cycles of 5-fluorouracil (500 mg/m^2), epirubicin (90 mg/m^2), and cyclophosphamide (500 mg/m^2) (FEC) or 4 cycles FEC followed by one cycle of high-dose chemotherapy consisting of cylophosphamide 6 g/m^2, thiotepa 480 mg/m^2 and carboplatin 1600 mg/m^2 over 4 days and autologous peripheral-stem cell re-infusion. The original protocol included tamoxifen, 40 mg daily for 2 years. During the trial, it became clear that 5 years tamoxifen was superior to 2 years. Patients with hormone-receptor-positive cancer therefore continued to receive tamoxifen for, in total, 5 years.[11]

The Medical Ethical Committee of the participating hospitals approved the study and all patients gave informed consent.

Health Related Quality of Life measures

HRQoL was assessed by means of a Visual Analogue Scale (VAS) for general health perception, the Short-Form 36 Health Survey (SF-36), and the Rotterdam Symptom Checklist (RSCL). The VAS scale ranged from 0 (worst imaginable health state) to 100 (best imaginable health state).

The SF-36 is organized into 8 scales assessing physical functioning, role-physical, bodily pain, general health, mental health, role-emotional, social functioning, and vitality.[13] Scale scores range from 0-100, with higher scores representing a higher level of functioning. Reference data for healthy Dutch women, mean age 47 years (range 16-96) were available for comparison.[14] The outcome of the SF-36 is age dependent. The age distribution in this study is skewed (range 24-56 years). Therefore, six age-categories were identified. Within each age category one “reference healthy woman” could be sampled for every four breast cancer patients. This way 199 reference women were identified and their data on the 8 scales of the SF-36 were used. The calculated mean values were used as references values.

The RSCL is a cancer-specific tool to measure psychological and physical distress in cancer patients. Patients indicated the degree to which they have been bothered by the 30 indicated symptoms in the past week.[15] The distribution of the RSCL item scores was highly skewed. Therefore, the 4-point Likert-type response scales were collapsed into the presence/absence of each symptom. Socio-demographic characteristics including age, education, marital status, number of children living at home and employment status were collected at baseline.

Follow-up

Patients received the questionnaires by mail before randomization, after chemotherapy completion, after radiotherapy completion and thereafter every 6

months. The data reported cover a maximum of 5 years post-randomization (maximum of 12 assessments).

Statistical analysis

The planned sample size was based on the primary endpoints: disease-free and overall survival. The HRQoL data were analyzed according to the intention-to-treat principle. Data of patients that had not yet reached the 5-years follow-up were included in the analysis until their last follow-up. Questionnaires of patients who relapsed or died within 5 years after randomization, were included in the analyses until disease relapse or death. Statistical analysis was performed using SPSS (11.0) and Multi Level-wiN (ML-Win) version 1.10.[16]

Student's t-test for independent samples and chi-square test were used to compare sociodemographic and baseline HRQoL scores of the two arms. At one year follow-up, Student's t test was used to compare mean SF-36 scores of the two arms with those of the age-matched reference group from the general Dutch population.

Mixed-effects analysis of variance models for repeated-measures was used to assess longitudinal HRQoL changes within and between treatment arms.[17] At randomization there was no difference in HRQoL between the two groups. This information was put into the mixed-effects analysis. Age (> 50 and ≤ 50 years) and menopausal status were separately included as covariates. A P value of $<.05$ was considered statistically significant.

Effect size is defined as the mean HRQoL scores difference between high-dose and conventional-dose group divided by the standard deviation of the HRQoL scores of the total group at that measurement moment. A value of 0.2-0.5 is considered indicative of a small effect, 0.5 a medium and 0.8 a large effect size.[18]

RESULTS

Patients

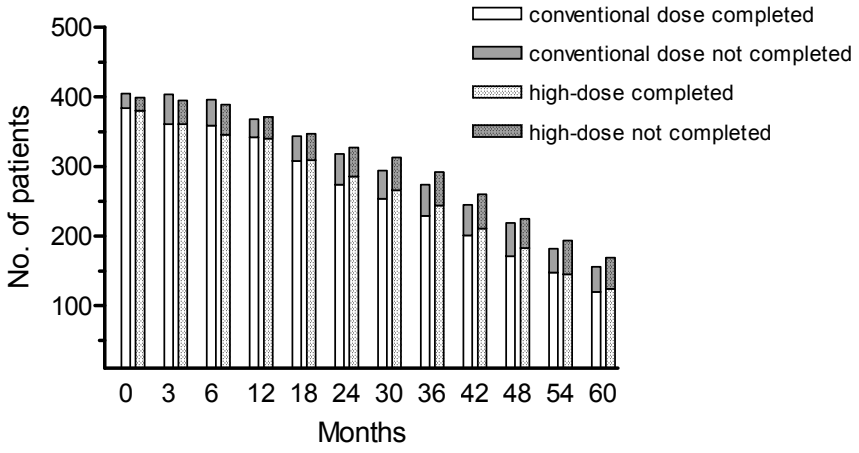
From August 1993 to July 1999, 885 patients were enrolled in the clinical trial.[11,12] The HRQoL component of the trial began after 47 patients had been entered. Of the remaining 838 patients, 34 (4%) did not participate (27 declined, 7 for logistical reasons). Of the 804 patients who participated in the HRQoL study, 405 received conventional-dose and 399 high-dose chemotherapy. Forty-one patients randomized to high-dose therapy did not receive this treatment.[11] According to the intention-to-treat principle, they were included in

the high-dose arm for analysis. None of the patients randomly assigned to conventional-dose received high-dose chemotherapy.

Compliance with HRQoL questionnaires

HRQoL data collected up to 5 years post-randomization were included in the analysis. The median follow-up was 57 months. Figure 1 shows response rates for the HRQoL questionnaires at baseline and during follow-up. The overall response rate was 86% (range 73-95%) at the various assessment points. No significant differences in compliance were observed between the treatment arms. 204 patients (25%, 100 in conventional-dose and 104 in high-dose group) had not yet reached the 5-years follow-up. At the time of analysis 325 (40%) patients (156 in conventional-dose and 169 in high-dose group) were disease-free at 5 years follow-up.

Figure 1. Number of patients in the conventional-dose and the high-dose treatment group that returned the HRQoL questionnaire during treatment and follow-up.



Sociodemographic characteristics

Patient characteristics at randomization were well balanced between the treatment arms (Table 1). At randomization 50% (n=400) of the patients were employed and 80% (n=646) had children. There were no significant differences between the arms in the percentage employed at randomization or at 1 or 3 years post-randomization, or in the number of hours per week worked. At follow-up, 34% of all patients reported working less (≤ 4 hours/week) than at trial entry, 48% indicated that this had not changed, and 18% worked more.

Table 1. Characteristics of the patients at randomization

	Conventional-dose group No. of patients	High-dose group No. of patients
Age (years)		
Mean	44.5	44.7
Range	26-56	24-56
Having a partner		
Yes	356	359
No	34	25
Unknown	15	15
Having children		
Yes	330	316
No	61	69
Unknown	14	14
Menopausal status		
Premenopausal	334	343
Postmenopausal	56	49
Uncertain	15	24
Education		
None		1
Grammar school	16	17
High-school	281	273
Entered some college	76	60
Completed college	17	34
Unknown	15	14

Health Related Quality of Life outcomes

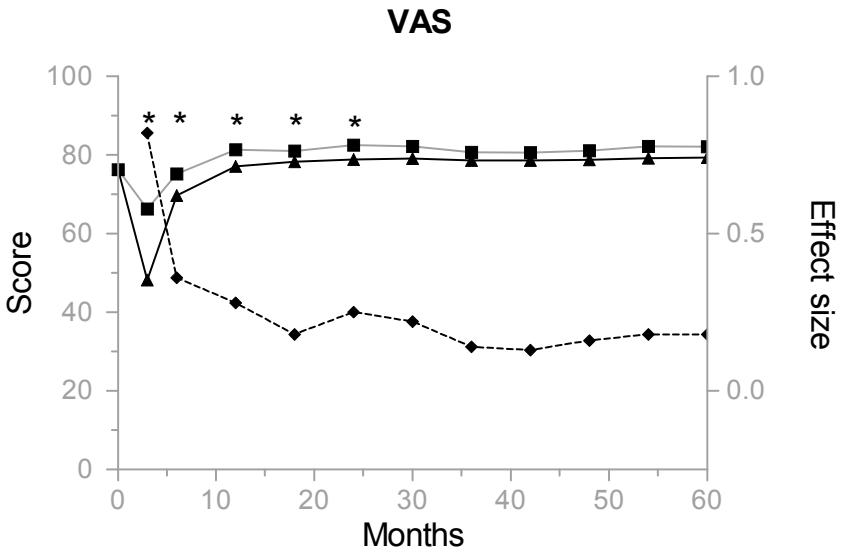
VAS

The results of the mixed-effects model analysis for VAS scores and effect sizes over time for both arms are illustrated in Figure 2. At baseline, there was no statistically significant difference in VAS scores between the treatment arms. Until 24 months the conventional-dose group scored statistical significant higher than the high-dose group. Just after chemotherapy there was a large effect size (0.82) and until 24 months a small effect size (0.18 to 0.36) was seen. Thereafter, no significant between group differences in VAS score were observed over time.

SF-36

The results of the mixed-effects models for all subscales during follow-up in both arms are presented in Figure 3, as well as the normal reference values and

Figure 2. Mean scores of the Visual Analogue Scale (VAS) by treatment group (high-dose (▲), conventional-dose (■) randomization and during 5 years (higher scores represent better quality of life) and the effect size (◆) The X-axis shows time in months. The left Y-axis represents the VAS score while the second Y-axis represents the effect size. Significant difference between the high-dose treatment group and the conventional-dose group is indicated with an asterisk (*)

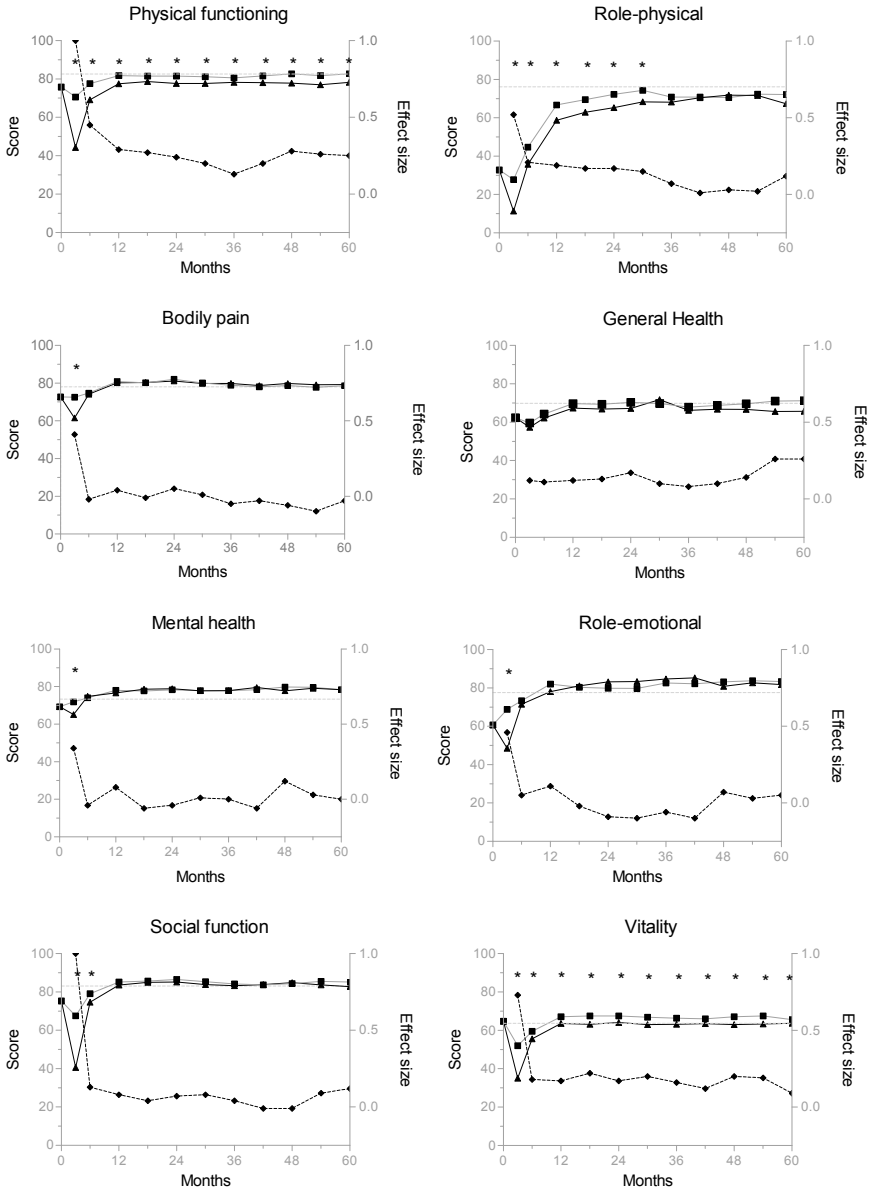


the effect sizes. At baseline, there were no significant differences between the arms in SF-36 scores. Both patient groups scored lower on two SF-36 scales, role-physical and role-emotional, than the general population reference sample. Directly after chemotherapy the high-dose group scored statistically significantly lower for all subscales, with effect sizes all above 0.5. Only the scores on general health did not differ between the two arms. For the scales: mental health, role-emotional, social functioning and bodily pain, no significant differences between the two arms were seen 6 months after randomization and later and effect sizes were always below 0.20.

During 2.5 years after randomization, the high-dose group had lower scores for role-physical compared to the conventional dose group but the effect sizes during this period were below 0.20.

For the scales physical functioning and vitality a small, but significant difference was observed between the two arms, during the 5 years follow-up. The effect sizes of physical functioning were during those years just above 0.20 and for vitality just below 0.20.

Figure 3. Mean scores of the SF-36 subscales in the high-dose treatment group (▲), conventional-dose treatment group (■), reference values from age corrected controls (---) and the effect size (◆), at randomization and during 5 years thereafter (higher scores represent a better quality of life). The X-axis shows time in months. The left Y-axis represents the VAS score while the right Y-axis represents the effect size. Significant difference between the high-dose treatment group and the conventional-dose group is indicated with an asterisk (*).

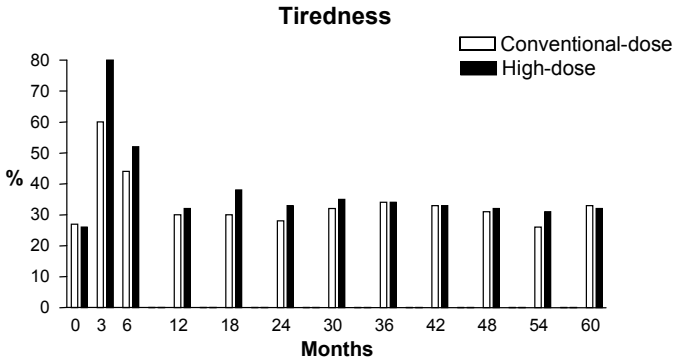


For all subscales, except for role-physical in both arms and physical functioning for the high-dose group, scores returned to normal or above reference values at 1 year. Thereafter, all HRQoL scores remained stable over the next 4 years.

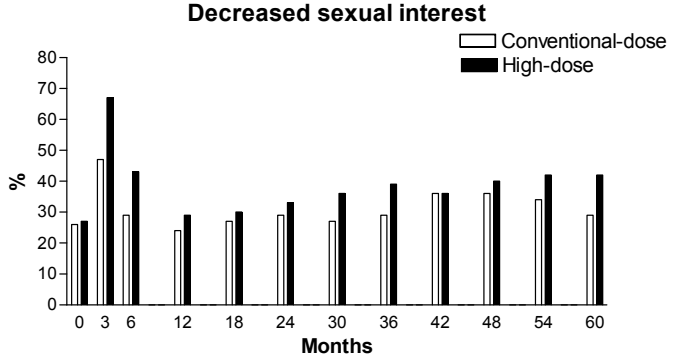
Correlation between age, menopausal status in the SF-36 and VAS scores

The covariates age and menopausal status had significant effect on the subscales physical functioning and role-physical. In both arms physical functioning scores of younger women (< 50 years at randomization) were significantly higher compared with older women at all time points. From 1 to 5 years after randomization, differences between younger and older women were statistically significant, but effect sizes were small. Patients who were

Figure 4. Percentage of patients reporting symptoms by the RSCL (3 = quite a bit, 4 = very much) at each assessment point for patients treated with conventional- or high-dose chemotherapy.



No. Responding Patients												
Conventional dose	383	359	359	340	308	274	255	230	211	177	158	129
High-dose	380	360	345	340	311	285	263	243	220	194	159	134



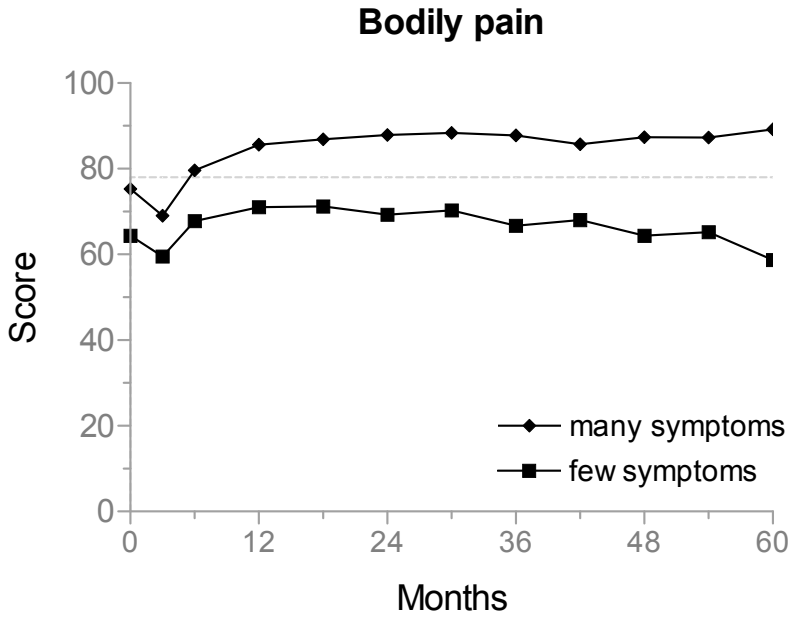
No. Responding Patients												
Conventional dose	379	353	354	340	305	272	253	228	199	169	145	119
High-dose	379	351	336	333	306	280	258	241	209	181	142	123

postmenopausal at randomization, scored significantly lower on the role-physical scale, compared with patients who were pre-menopausal over the whole 5 year period.

Rotterdam Symptom Checklist (RSCL)

Tiredness, decreased sexual interest, sweating and painful muscles were the most prevalent symptoms. The percentage of patients reporting tiredness and decreased sexual interest over time is shown in Figure 4. Just after chemotherapy, the percentage of patients with physical symptoms was higher compared with baseline in both arms. Overall, the percentage of patients with symptoms was higher in the high-dose group. This difference was already largely reduced 6 months after randomization. During the follow-up period 10% of the patients (n=78) experienced three or four of the most prevalent symptoms for more than half of the time. Compared to patients without this high frequency of complaints, these patients could only be distinguished by a lower education level. The seven items indicating psychological distress (irritability, worrying, depressed mood, nervousness, despairing about the future, tension, anxiety) diminished in both arms from randomization up to 1 year later and remained constant over the next 4 years. After 5 years 244

Figure 5. Mean scores of the SF-36 subscales bodily pain for the patients with with many (≥ 4) (◆) and few (≤ 3) symptoms (■) and the reference values from age corrected controls (---) at randomization and during 5 years thereafter (higher scores represent a better quality of life). The X-axis shows time in months. The left Y-axis represents the bodily pain score.



patients completed HRQoL questionnaires and 33% of them reported no symptoms, 17% experienced one, 13% two, 9% three and 28% four or more symptoms of the RSCL.
Decreased sexual interest was the most prevalent symptom (36%). Patients with many (≥4) and few symptoms (≤3) showed no differences with regard to treatment arm, age, employment status, number of working hours at randomization, having children and children living at home, marital status, menopausal status at randomization or education level. Patients with many symptoms after 5 years scored significantly lower on all SF-36 subscales at randomization and at the 11 measurement points thereafter compared with other patients. The only exception was role-physical at randomization. In Figure 5 the scores over time for the subscale bodily pain for the patients with many and few complaints is shown. The results for other subscales of SF-36 and VAS are comparable and not shown. Eighty percent of patients scoring ≤3 symptoms of the RSCL at randomization report ≤3 complaints after 5 years and half of all patients scoring ≥4 items at randomization score ≥4 symptoms.

DISCUSSION

This prospective, longitudinal study describes HRQoL for 5 years following randomization between conventional and high-dose chemotherapy in a large group of disease-free, high-risk breast cancer patients. At randomization, their HRQoL was only slightly different from an age- and gender-matched control group obtained from the general Dutch population. During the immediate post-treatment period, HRoQL was worse in the high-dose than in the conventional-dose treatment group. However, 1 year after randomization, HRQoL in both groups was again comparable to the general population reference values, and these levels remained relatively constant over the next 4 years.
Comparison of HRQoL studies is relevant but can be hampered by differences in study designs and measures used.[19] In the future, disease-specific questionnaires like FACT-B, might be able to detect additional differences which e.g. the SF-36 does not reveal.
A small cross-sectional study in 43 patients with 2 years median follow-up after high-dose chemotherapy reported higher HRQoL scores compared to patients with conventional-dose chemotherapy using the Functional Living Index Cancer questionnaire (FLIC). This FLIC score differed, however, only marginally between the two groups.[20] Another study, comparing pre- and post treatment HRQoL, observed that disease-free breast cancer patients (n=24) following high-dose chemotherapy had higher HRQoL than prior to treatment.[3] They excluded all

patients who relapsed or died during follow-up from the analysis. In order to achieve an objective rating of HRQoL, data of all patients were included in our study until disease relapse or death.

Although research on HRQoL in breast cancer patients has become increasingly sophisticated, few longitudinal studies assessed patients before and after treatment.[7,9,10,21] Longitudinal HRQoL studies lay a considerable claim to the compliance of patients, requiring frequent HRQoL questionnaires to be returned.[6] Objectively and compared with others, our overall response rate was high (86%).[7,9,10] Most longitudinal HRQoL studies are analyzed with repeated measurement ANOVA, and one missing questionnaire will result in omitting all data of that particular patient. Analysis by mixed-effect models as performed in our study has the advantage that all data can be used and selection bias is excluded.

One large randomized prospective study, with serial assessment points, compared HRQoL of adjuvant high-dose (n=197) with "tailored" chemotherapy (n=211). This study showed a larger decrease in HRQoL and faster recovery in the high-dose group compared to the "tailored" group during the first year.[7] Similar to our findings, HRQoL had returned to baseline in both groups 1 year after treatment. The faster HRQoL recovery in their high-dose group found can be explained by the fact, that the tailored arm actually had received more chemotherapy over a longer period of time.[7] Another prospective study compared HRQoL of breast cancer patients until 3 years after high-dose (n=106) with intermediate-dose chemotherapy (n=104). HRQoL was compromised transiently among patients in the high-dose but not in the intermediate-dose group.[10] One explanation for this finding could be the fact that the first assessment took place 3 months after chemotherapy, thereby missing the transient fall in the HRQoL in the intermediate-dose group. Availability of HRQoL data of healthy women allowed us to interpret HRQoL in a more balanced manner. HRQoL of our patients appeared to be comparable to that of healthy women of the same age. With frequent assessments, others found a decrease in HRQoL in both arms, similar to our observations.[7] In another prospective longitudinal breast cancer study in 52 patients after high-dose chemotherapy HRQoL were measured repeatedly from baseline over 2 years. HRQoL decreased but had returned to baseline 8 weeks post treatment.[9] Although our and the above studies differ in many aspects, 1 year after treatment no differences in HRQoL between the treatment groups or baseline were found by all four.[7,9,10]

In our study patients generally reported a few (late) symptoms, but some complaints persisted several years. Remarkably, single symptoms apparently did not have a severe influence on the HRQoL. Decreased sexual interest was the most prevalent symptom. Impaired sexual functioning represents a well-known

specific long-term sequel of breast cancer patients.[4,9,22,23] This can be partly due to chemotherapy causing premature ovarian failure.[9] Tiredness, painful muscles and sweating were also frequently reported. Interpreting these results is difficult because healthy postmenopausal women also commonly mention these symptoms. We have earlier shown that (lower) mental health was the strongest predictor for tiredness in a sub-population of the current study.[24] Patients with repeated multiple complaints were in the current analysis, characterized by a lower educational level. A few other studies also observed this relation. Kornblith et al noticed that breast cancer survivors with a lower education level had more problems adapting to posttraumatic stress 20 years after adjuvant therapy.[25] In a study of 2,208 women with breast cancer or at risk for breast cancer detected that women with a lower educational level were more likely to be bothered by symptoms.[26] In our study the 10% of the patients with repeated multiple complaints are characterized by a lower education level. We also analyzed for 5 year disease free survivors whether complaints mentioned in the RSCL at randomization predicted their HRQoL at 5 years. This revealed that half of those with four or more symptoms at 5 years also had many complaints at randomization. This indicates that having complaints before chemotherapy predicts a worse HRQoL outcome.

HRQoL of breast cancer patients in our study, 1-5 years after treatment, is comparable to healthy women. Only small, clinically irrelevant differences were observed between the treatment groups. The impact of both chemotherapy regimes on HRQoL is therefore clearly less severe than expected. HRQoL recovers swiftly after adjuvant treatment. Women with poor prognosis breast cancer, engaged in intensive treatment protocols, tend to adapt to their new situation and to modify their reference points. The emotional and social support of relatives, friends and medical staff, can contribute to their adaptation.[27] Identifying patients who have a higher chance of persistent impaired quality of life after treatment may open the way for better patient-tailored prevention strategies.

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