Neuropsychological function in high-risk breast cancer survivors after stem-cell supported high-dose therapy versus standard-dose chemotherapy: evaluation of long-term treatment effects

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Background: Studies on cognitive functioning in breast cancer patients point out that a subset of women exhibit chemotherapy-related neuropsychological impairment. Thereby, high-dose therapy may elevate the risk of cognitive dysfunctions. The primary purpose of the study was to evaluate the impact of high-dose versus standard-dose chemotherapy on the late neuropsychological outcome in randomized assigned high-risk breast cancer survivors. Next to focusing prevalence, function specificity and extent of cognitive impairment, the question as to whether doses-dependant group differences occur was investigated.

Patients and methods: Twenty-four high-dose and 23 standard-dose patients 5 years, on average, after treatment underwent a comprehensive neuropsychological assessment. In addition, 29 early-stage breast cancer patients matched for age, education and time since treatment were recruited as a comparison group.

Results: Global cognitive impairment was observed in 8% of high-dose versus 13% of standard-dose compared with 3% of early-stage breast cancer patients. Compared with normative data, all patient groups performed worse on one attention subtest measuring the simple reaction time (P < 0.001 in each case). By contrast, no significant between-group differences on the late neuropsychological outcome were found.

Conclusions: Five years after treatment, standard-dose patients were slightly, but not significantly, more impaired in cognitive performance than high-dose patients.

Key words: breast cancer, cognitive function, high-dose chemotherapy, long-term treatment effects, neuropsychological outcome

introduction

Chemotherapy-induced neuropsychological impairment as a possible side-effect of systemic cancer treatments and one important issue of a patients' quality of life has been investigated in several cross-sectional studies with breast cancer patients [1–8]. Moreover, in women with high-risk breast cancer, the extent of cognitive dysfunction has been discussed against the background of different treatment regimens [2, 5]. Overall, studies point out that both adjuvant standard-dose regimens, as well as high-dose therapy with autologous hematopoietic stem-cell support as a further treatment option for high-risk breast cancer patients, can lead to impairments in neuropsychological functioning. It has consistently been shown that a subgroup of women is at risk exhibiting cognitive dysfunction in the course of chemotherapy [4] as well as after completion of treatment. Van Dam and colleagues [2] investigated the neuropsychological outcome in high-risk breast cancer patients either treated with stem-cell supported high-dose therapy or standard-dose chemotherapy compared with early-stage breast cancer patients at an average of 2 years since completion of last therapy. Cognitive impairment was observed in 32% of high-dose patients, 17% of standard-dose patients and 9% of control patients. In addition, high-dose patients demonstrated an 8.2-times higher risk for cognitive dysfunction compared with the control group and a 3.5-times higher risk compared with the standard-dose patients, while the authors noted that the latter effect did not reach statistical
significance. These findings suggest that high-dose therapy is more prone to precipitate neuropsychological impairment than standard-dose chemotherapy. In a neuropsychological follow-up study conducted by Schagen et al. [5], differences in cognitive functioning between the three patient groups were no longer observed when re-examined an average of 4 years after treatment. Test results of both the high-dose patients and the standard-dose patients improved whereas they slightly deteriorated in control patients. Out of all patients who participated on the first and the follow-up assessment, 14% of high-dose patients and 9% of standard-dose patients were classified as cognitively impaired compared with 11% of the controls. The authors point out that cognitive impairment following chemotherapy might be a transient phenomenon. In contrast, Ahles and colleagues [6] found cognitive dysfunction in long-term survivors of breast cancer and lymphoma at an average of 10 years after standard-dose chemotherapy compared with local therapy patients. When categorized by their neuropsychological performance, patients treated with chemotherapy showed significantly lower scores in comparison with the local therapy group (39% versus 14%).

The most frequently reported cognitive domains being vulnerable to chemotherapy are attention, memory and executive functions. Cognitive impairment in these domains can lead to difficulties with activities of daily living and working life and, therefore, have a high relevance for the patients concerned. In a recently published meta-analysis on treatment-related cognitive dysfunction in adult cancer patients [9], the largest significant negative effect sizes were found for the domains of executive functions and verbal memory when patients were compared with normative data.

The inconsistent findings concerning long-term treatment effects of different types of adjuvant chemotherapy regimens in breast cancer survivors emphasize the need for further research. The purpose of the present study was to evaluate the impact of stem-cell supported high-dose therapy versus standard-dose chemotherapy on the late neuropsychological outcome in a German population of high-risk breast cancer patients compared with early-stage breast cancer survivors. The study focused on the assessment of prevalence, function specificity and extent of cognitive impairment as well as on answering the question of whether there is evidence for a treatment-related doses-effect 5 years, on average, since completion of treatment.

**patients and methods**

**background**

All high-risk breast cancer survivors investigated in the present study had participated in a prospective multi-center randomized trial [10] comparing the therapeutic effects of high-dose therapy versus adjuvant standard-dose chemotherapy as treatment options with respect to event-free survival: axillary lymph node-positive (pN ≥ 10) patients between 18 and 60 years of age with primary breast carcinoma and absence of distant metastases were included. Patients were treated according to the study protocol as follows: after surgery (mastectomy or breast-conserving) and four cycles of EC chemotherapy (epirubicin 90 mg/m² and cyclophosphamide 600 mg/m², intravenously every 21 days) patients were randomized to receive either three cycles of standard-dose CMF chemotherapy (cyclophosphamide 500 mg/m², methotrexate 40 mg/m² and 5-fluorouracil 600 mg/m², intravenously on days 1 and 8 every 28 days) or high-dose CTM chemotherapy (cyclophosphamide 1500 mg/m², thiotepa 150 mg/m² and mitoxantrone 10 mg/m², intravenously for four consecutive days) followed by autologous hematopoietic stem-cell support. In addition, most women had received locoregional radiation therapy. Hormone receptor-positive breast cancer patients were treated with tamoxifen (20 mg daily) for 5 years.

**study participants**

An average of 5 years after completion of high-dose regimen (n = 24) or standard-dose chemotherapy (n = 23), high-risk breast cancer patients were recruited from three university clinics and one community hospital in Germany. Women who fulfilled the following criteria were excluded: current or interim chemotherapy subsequent to high-dose or standard-dose regimen, current radiation therapy, history or presence of neurological disorders, current use of psychoactive medication, substance abuse, non-fluent in speaking and reading German, uncorrected vision. In the participating centers, a total number of 140 high-risk breast cancer patients had been treated according to the study protocol of the randomized trial. Among these women, 47 (34%) had died and 26 (19%) fulfilled the exclusion criteria. Of the remaining eligible 67 patients, 12 (18%) declined to participate, six (9%) had moved to an unknown address, two (3%) could not be scheduled for organizational reasons and 47 (70%) agreed to participate.

In addition, a comparison group, matched for age, education and time since treatment, was drawn from the population of patients treated for early-stage breast cancer at the Hamburg-Eppendorf University Medical Center. Women previously treated with surgery and radiation therapy for stage I or II breast cancer (non-chemotherapy patients) were identified in cooperation with the radiology team. Exclusion criteria were the same as for high-risk patients. Among a total of 57 early-stage breast cancer survivors, five (9%) fulfilled the exclusion criteria. Of the eligible 52 women, nine (17%) could not be reached, eight (15%) refused to participate, six (12%) could not be scheduled because of organizational problems and 29 (56%) participated in our study.

Patients who gave informed consent to participate were scheduled for neuropsychological assessment at their local medical treatment center. Neuropsychological testing was carried out from November 2002 to April 2004 by trained and experienced neuropsychologists.**

**measures**

Patients underwent a comprehensive neuropsychological assessment across the cognitive domains attention, memory and executive functions, which took less than 2 h. The test battery consisted of frequently used standardized psychometric tests with published normative data, which are used either in international research on cognitive functioning in cancer patients or in the context of clinical routine neuropsychological assessment in Germany [11–18]. In order to estimate the premorbid intelligence level the subtest ‘general knowledge’ of the revised Hamburg–Wechsler Intelligenztest für Erwachsene (HAWIE-R) [19] was administered. Table 1 shows the tests applied as well as the specific cognitive functions and superior domains they had been validated for. Test assignments to function-specific subdomains were carried out following national recommendations for clinical neuropsychological assessment [20, 21].

Demographic and treatment-related variables were obtained through the use of a standardized questionnaire, by a semi-structured interview, and by medical records.

**definition of neuropsychological impairment**

Eighteen test parameters were included in the final analyses. To enable comparability and interpretation of test results, raw scores were transformed or converted into standard z-scores. Since neuropsychological impairment
in the comparison group could not be excluded, means and standard deviations (SD) of the published test norms were used as a reference for the transformation procedure.

Following the Compendium of Neuropsychological Tests [22], a z-score of \(z \leq -1.4\) SD below the mean of zero was defined as cut-off for neuropsychological impairment in a test parameter and specific cognitive function, respectively. This cut-off corresponds to a percentile rank of \(\leq 58\%\). In addition, for each patient a global impairment score was calculated by summing up all test parameters in the impaired range specified above. In order to classify a patient as being impaired in this overall measure, a second cut-off was defined that corresponds to the number of impaired parameters on the fifth percentile of the comparison group [2, 5]. According to this definition, patients exhibiting four or more test parameters in the impaired range were classified as being impaired in their global neuropsychological performance.

**statistical analysis**

Data analyses were performed with the Statistical Package for the Social Sciences (SPSS) for Windows, version 11.5.1. Descriptive statistics included analyses regarding demographic and treatment-related data, but particularly focused on the calculation of prevalences for neuropsychological impairment. Prevalence rates were computed separately for each group and level (i.e. specific function, cognitive domain, global outcome). The Shapiro-Wilk’s W-test was conducted to verify the assumption of normal distribution. All analyses of test parameters were performed using z-scores corrected for age, gender and education, which leads to variance reduction compared with raw scores. To compare group z-mean scores of normally distributed parameters with the population parameter, the one-sample t-test was used. Furthermore, analysis of variance (ANOVA) was conducted for between-group comparisons. For parameters not following the normal distribution, differences between groups were analyzed by the Kruskal-Wallis test. Concerning the variable ‘impairment’, statistical analyses were calculated with the \(\chi^2\)-test for 2 \(\times\) 3 contingency tables. Whenever more than 20% of the cells had an expected frequency of less than 5, Fisher’s exact test was performed. Two-tailed significance tests were conducted using a significance level of \(P < 0.05\). To adjust \(P\) values for multiple comparisons, the Bonferroni correction was used.

**results**

Demographic and treatment-related characteristics of the patient groups are presented in Table 2. The three groups of breast cancer patients did not significantly differ regarding age \([\chi^2 (2, n = 76) = 1.76, P = 0.41]\), level of education \([\chi^2 (2, n = 76) = 0.53, P = 0.77]\), estimated premorbid intelligence level \([\chi^2 (2, n = 76) = 0.52, P = 0.77]\), current use of tamoxifen \([\chi^2 (2, n = 76) = 5.47, P = 0.07]\) and time since last treatment \([\chi^2 (2, n = 76) = 0.67, P = 0.71]\). In all patient groups, an estimated premorbid intelligence level in the normal range was observed. In order to examine the representativity of the study sample (all high-risk breast cancer patients), study participants \((n = 47)\) were compared with those patients who did not agree to participate \((n = 12)\). No significant differences were seen in terms of age \((U\text{-test, } P = 0.58)\) and type of treatment \([\chi^2 (1, n = 59) = 0.004, P = 0.95]\).

**function-specific neuropsychological outcome**

Comparisons of group z-mean scores with the population parameter revealed significant differences on some
function-specific subtests of the attention and executive functions domains (Table 3). After Bonferroni correction, performance on the subtest simple reaction time remained worse in all three patient groups \( (P < 0.001 \text{ in each case}). \) In addition, high-dose patients demonstrated a lower performance on the selective attention Test d2 \( (P = 0.001). \) Substantially higher z-mean scores were obtained in the standard-dose group on both reasoning subtests \( (P < 0.001 \text{ in each case}) \) as well as in the comparison group on the category word fluency subtest \( (P < 0.001) \) and the reasoning subtest LPS-4 \( (P < 0.001). \)

There were no significant differences between the three patient groups in z-mean scores and z-mean ranks, respectively, on any of the test parameters (Tables 4, 5). Therefore, cognitive dysfunction on an individual level was detected by calculating impairment scores for each parameter and patient. Absolute and relative frequencies according to the defined cut-off for neuropsychological dysfunction on a test parameter are presented in Table 6. In each group, patients were mostly impaired on the attention parameter simple reaction time. Moreover, there was a non-significant trend towards poorer outcomes in selective attention (Test d2) for patients in the chemotherapy groups. There was also a non-significant trend for women after standard-dose treatment to have an increased impairment rate on the letter fluency subtest than high-dose and comparison patients. As a consistent result in all groups, no impairment occurred on the two reasoning subtests LPS-3

### Table 2. Demographic and treatment-related characteristics

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>Mean age, years (SD)</th>
<th>Level of education, %b</th>
<th>Premorbid intelligence, mean IQ scoreg (SD)</th>
<th>Current use of tamoxifen, %h</th>
<th>Mean time since last treatment, months (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard-dose</td>
<td>51.8 (8.6)</td>
<td>34.8</td>
<td>103.1 (15.9)</td>
<td>43.5</td>
<td>62.2 (22.7)</td>
</tr>
<tr>
<td>High-dose</td>
<td>53.3 (7.1)</td>
<td>41.7</td>
<td>104.9 (14.4)</td>
<td>50.0</td>
<td>61.6 (21.7)</td>
</tr>
<tr>
<td>Comparison</td>
<td>54.6 (8.0)</td>
<td>31.0</td>
<td>103.1 (10.3)</td>
<td>20.7</td>
<td>63.5 (14.0)</td>
</tr>
<tr>
<td>P value4</td>
<td>0.41</td>
<td></td>
<td>0.77</td>
<td></td>
<td>0.71</td>
</tr>
</tbody>
</table>

SD, standard deviation.

kKruskal–Wallis test; significance level \( P < 0.05. \)

bThe sum of percentages does not always equal 100% due to rounding errors; \( P = 0.77. \)

c9 years of education.

d10 years of education.

eHigh-school graduation.

fCollege graduate.

gIQ scale: mean, 100; SD, 15. The premorbid intelligence level was measured using the subtest general knowledge of the HAWIE-R.

h\( P = 0.07. \)

### Table 3. Comparisons of z-mean scores with the population parameter

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>Attention</th>
<th>Executive functions</th>
<th>Adjusted alpha level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Selective attentiona</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple reaction timeb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive functions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category word fluencyc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reasoningd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reasoninge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard-dose</td>
<td>−0.64 (1.19)</td>
<td>−0.86 (0.75)</td>
<td>0.57 (1.31)</td>
</tr>
<tr>
<td>( (n = 23) )</td>
<td>( P = 0.02 )</td>
<td>( P &lt; 0.001 )</td>
<td>( P &lt; 0.05 )</td>
</tr>
<tr>
<td>High-doseg</td>
<td>−0.64 (0.85)</td>
<td>−0.82 (0.74)</td>
<td>n.n.d.</td>
</tr>
<tr>
<td>( (n = 24) )</td>
<td>( P = 0.001 )</td>
<td>( P &lt; 0.001 )</td>
<td>( P = 0.03 )</td>
</tr>
<tr>
<td>Comparison</td>
<td>−0.26 (0.62)</td>
<td>−0.76 (0.60)</td>
<td>0.91 (1.02)</td>
</tr>
<tr>
<td>( (n = 29) )</td>
<td>( P = 0.04 )</td>
<td>( P &lt; 0.001 )</td>
<td>( P &lt; 0.001 )</td>
</tr>
</tbody>
</table>

SD, standard deviation; n.n.d., not normally distributed parameter in this patient group. Standard z-scores: mean, 0; SD, 1.

aTest d2; comparison group: \( n = 28. \)

bTAP.

cRWT.

dLPS-3; standard-dose group: \( n = 22. \)

eLPS-4; standard-dose group: \( n = 22. \)

fOne-sample t-test; significance level \( P < 0.05. \)

Additionally, the z-mean score of the test parameter phasic alertness (TAP) is lower than the population parameter \( (P = 0.03). \)
and LPS-4. To summarize, with regard to the function-specific outcome no significant group differences were observed (Table 6).

domain-specific neuropsychological outcome

The domain-specific outcome rates are presented in Table 7. Among high-risk patients, most impairments were observed on attention parameters. About half of the women after standard-dose and high-dose treatment performed in the impaired range on at least one of the six attention parameters compared with 28% \( (n = 8) \) of the non-chemotherapy patients. However, differences failed statistical significance. Cognitive dysfunction on memory subtests was also frequent (about one-third of the patients in each group was impaired), but considering that the total number of parameters comprising the memory domain is greater, not to that extent seen in the attention domain.

Performance on parameters from the executive functions domain was least affected as no patient had scored in the impaired range on more than one of the four subtests. Again, no significant group differences were seen either with respect to the observed frequencies of impairment (Table 7) or regarding the number of affected parameters in each domain (data not shown).

global neuropsychological outcome

In the standard-dose and high-dose groups, a total number of seven and four impaired parameters, respectively, was observed compared with a maximum of four impaired

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**Table 4. Z-mean scores and standard deviations of normally distributed parameters**

<table>
<thead>
<tr>
<th>Specific cognitive function (parameter, test)</th>
<th>Standard-dose ( (n = 23) ) Mean (SD)</th>
<th>High-dose ( (n = 24) ) Mean (SD)</th>
<th>Comparison ( (n = 29) ) Mean (SD)</th>
<th>( F ) value(^a)</th>
<th>( P ) value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple reaction time (median time, alertness TAP)</td>
<td>(-0.86) (0.75)</td>
<td>(-0.82) (0.74)</td>
<td>(-0.76) (0.60)</td>
<td>0.14</td>
<td>0.87</td>
</tr>
<tr>
<td>Phasic alertness (parameter alertness, TAP)</td>
<td>(0.06) (0.94)</td>
<td>(-0.37) (0.79)</td>
<td>(-0.03) (0.74)</td>
<td>1.85</td>
<td>0.17</td>
</tr>
<tr>
<td>Selective attention (median time, Go/Nogo TAP)</td>
<td>(-0.29) (0.79)</td>
<td>(0.02) (0.83)</td>
<td>(-0.12) (0.84)</td>
<td>0.83</td>
<td>0.44</td>
</tr>
<tr>
<td>Selective attention (GZ–F, Test d2)</td>
<td>(-0.64) (1.19)</td>
<td>(-0.64) (0.85)</td>
<td>(-0.26) (0.62)(^c)</td>
<td>1.57</td>
<td>0.22</td>
</tr>
<tr>
<td>Verbal working memory (digit span forward, WMS-R)</td>
<td>(0.31) (1.20)</td>
<td>(0.08) (1.20)</td>
<td>(0.02) (0.80)</td>
<td>0.49</td>
<td>0.61</td>
</tr>
<tr>
<td>Visuo-spatial working memory (visual span forward, WMS-R)</td>
<td>(0.27) (1.27)</td>
<td>(0.13) (1.35)</td>
<td>(0.26) (1.07)</td>
<td>0.10</td>
<td>0.90</td>
</tr>
<tr>
<td>Verbal learning (DG1-5, VLMT)</td>
<td>(0.21) (1.04)</td>
<td>(0.23) (0.98)</td>
<td>(0.25) (0.82)</td>
<td>0.01</td>
<td>0.99</td>
</tr>
<tr>
<td>Verbal retroactive interference (DG5-DG6, VLMT)</td>
<td>(-0.06) (0.88)</td>
<td>(0.12) (0.81)</td>
<td>(-0.10) (0.84)</td>
<td>0.47</td>
<td>0.63</td>
</tr>
<tr>
<td>Visual delayed recall (30-min delay, ROCFT)</td>
<td>(0.24) (0.79)</td>
<td>(0.25) (0.82)</td>
<td>(0.12) (0.87)</td>
<td>0.19</td>
<td>0.83</td>
</tr>
<tr>
<td>Letter fluency (no. of correct responses, RWT)</td>
<td>(0.02) (1.22)</td>
<td>(0.12) (0.87)</td>
<td>(0.15) (0.77)</td>
<td>0.12</td>
<td>0.88</td>
</tr>
<tr>
<td>Reasoning (no. of correct items, LPS-3)</td>
<td>(0.72) (0.75)(^d)</td>
<td>(0.36) (0.76)</td>
<td>(0.32) (0.80)</td>
<td>1.96</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Percentile ranks of median reaction times (TAP parameters) were converted into z-scores, which were therefore normally distributed; the 11 parameters shown are normally distributed in all patient groups.

SD, standard deviation; GZ–F, total number of items completed minus total number of errors; DG1-5, sum of correct items on the learning trials 1 to 5; DG5-DG6, sum of correct items on learning trial 5 (DG5) minus sum of correct items on the immediate recall (DG6) after interference trial.

\(^a\)Analysis of variance (ANOVA).
\(^b\)Significance level = \( P < 0.05 \).
\(^c\)\( n = 28 \).
\(^d\)\( n = 22 \).

**Table 5. Z-mean rank scores of not normally distributed parameters**

<table>
<thead>
<tr>
<th>Specific cognitive function (parameter, test)</th>
<th>Standard-dose ( (n = 23) ) Mean rank</th>
<th>High-dose ( (n = 24) ) Mean rank</th>
<th>Comparison ( (n = 29) ) Mean rank</th>
<th>( \chi^2 ) (2)(^a)</th>
<th>( P ) value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of information processing (time, TMT-A)</td>
<td>39.70</td>
<td>33.38</td>
<td>41.79</td>
<td>2.01</td>
<td>0.37</td>
</tr>
<tr>
<td>Divided attention/cognitive flexibility (time, TMT-B)</td>
<td>41.76</td>
<td>31.92</td>
<td>41.36</td>
<td>3.12</td>
<td>0.21</td>
</tr>
<tr>
<td>Verbal working memory (digit span backward, WMS-R)</td>
<td>34.76</td>
<td>42.23</td>
<td>38.38</td>
<td>1.35</td>
<td>0.51</td>
</tr>
<tr>
<td>Verbal delayed recall (30-min delay, DG5-DG7 VLMT)</td>
<td>38.85</td>
<td>39.46</td>
<td>37.43</td>
<td>0.12</td>
<td>0.94</td>
</tr>
<tr>
<td>Verbal recognition (W–F, VLMT)</td>
<td>40.35</td>
<td>40.50</td>
<td>35.38</td>
<td>0.95</td>
<td>0.62</td>
</tr>
<tr>
<td>Category fluency (no. of correct responses, RWT)</td>
<td>33.67</td>
<td>41.79</td>
<td>39.60</td>
<td>1.71</td>
<td>0.43</td>
</tr>
<tr>
<td>Reasoning (no. of correct items, LPS-4)</td>
<td>40.23(^c)</td>
<td>39.50</td>
<td>35.07</td>
<td>0.88</td>
<td>0.65</td>
</tr>
</tbody>
</table>

The seven parameters shown are not normally distributed in all patient groups.

SD, standard deviation; DG5-DG7, sum of correct items on learning trial 5 (DG5) minus sum of correct items on the delayed recall (DG7) after a 30-min delay; W–F, total number of correct items on the recognition trial minus total number of errors.

\(^a\)Kruskal–Wallis test.
\(^b\)Significance level = \( P < 0.05 \).
\(^c\)\( n = 22 \).
parameters in the comparison group. No significant between-group differences were found ($P = 0.14$).

Moreover, the fifth percentile of the distribution of test parameters in the impaired range of the comparison group was used to calculate the second cut-off score indicating the extent of overall neuropsychological dysfunction. The relative frequencies of global impairment in the three patient groups are shown in Figure 1. Standard-dose patients (13%) were slightly...
possibly lead to adverse effects on the central nervous system. Intrathecal MTX, but also conventional dosage of MTX might concomitantly applied cranial irradiation, high-dose or CMF regimen includes methotrexate (MTX) known as one of a dose-dependent late cognitive outcome. Among others, the support the assumption of a substance-dependent rather than neuropsychological dysfunction in the standard-dose patients. These patients, 13% versus 8%). In order to have a closer look at this result, the three groups of breast cancer patients did not significantly differ on any of the psychological measures mentioned above (data not shown). The results will be discussed in detail in a subsequent publication.

Least impairments were seen in the executive functions domain as no patient scored in the impaired range on the reasoning subtests. One possible interpretation of this unexpected result is that the tests selected have insufficient sensitivity and their usefulness in measuring subtle cognitive impairments therefore might be limited. Published normative data provided for the reasoning tasks were about 20 years old. Since IQ scores in populations have shown an increase over time [32], restandardization of such tests is frequently required because using obsolete norms can lead to incorrect interpretation of test results. Thus, subtle impairments on reasoning parameters might be undiscovered in our patients. However, these tasks were administered as no alternative psychometric tests measuring reasoning were available.

In another finding, consistent with the Dutch 4 years follow-up [5], no significant group differences in the late neuropsychological outcome were observed. Nevertheless, interpretation of these results is limited, as the authors considered that patients initially classified as cognitively impaired were inconsistently lost to follow-up among the chemotherapy groups. Hence, the absence of group differences could simply reflect the problem of dropout due to disease or refusal.

In general, comparability of study results on chemotherapy-related cognitive functioning in breast cancer patients is limited as long as different cut-off scores for
neuropsychological dysfunction are used and no global guiding principles concerning selection and domain assignment of subtests are clearly defined. Therefore, no neuropsychological impairment per se, but cognitive dysfunction according to a predefined cut-off and deviations from test norms, respectively, are measured.

The present study has several limitations. Because our sample size is small, caution in interpretation of neuropsychological outcome rates and not observed treatment-related group differences is needed. Moreover, although high-risk patients were randomly assigned to a treatment regimen, selectivity of the samples cannot be excluded. Women who participated in the prospective multi-center trial might differ in psychological variables from those who did not participate. As mentioned above, another problem could be based on the possibility that most impaired high-risk patients did not participate due to disease-related factors. A selection bias might also exist for the comparison subjects. These patients performed as poor as high-risk patients on the simple reaction time task and thus could not be used as a reference group on the function-specific level. Importantly, global prevalence rates among the high-risk patients, therefore, presumably reflect a lower boundary of late neuropsychological dysfunction, because performance might be overestimated in view of a similarly affected comparison group used as a reference on the global outcome level. A further study limitation is the cross-sectional post-treatment design. Due to the lack of baseline data indicating the premorbid level of global cognitive functioning in our chemotherapy patients, conclusions about treatment-related neuropsychological dysfunction in the course of time can hardly be drawn. Impairments can already occur before chemotherapy as was shown in two recently published studies on cognitive functioning in women with breast carcinoma [33, 34]. Therefore, prospective, longitudinal studies on this scope are needed to determine the extent to which neuropsychological performance is affected by chemotherapy and mediated by other confounding factors, respectively, over time. Even though there seems to be a differential effect of chemotherapy, treatment-related cognitive dysfunction in survivors may outline a growing problem in health care and rehabilitation, which has to be recognized and treated in time.

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references