Aim: We describe the impact of a sequential dose-dense schedule of carboplatin and paclitaxel on the quality of life (QoL) of patients with ovarian cancer. Patients and Methods: In this multicenter phase II trial, four cycles of carboplatin followed by 12 cycles of weekly paclitaxel were applied after cytoreductive surgery. QoL was assessed using the QoL questionnaires EORTC QLQ-C30 and QLQ-OV28 before chemotherapy (baseline), after four cycles of carboplatin, at the end of treatment (EOT), and after 6, 12, and 24 months. Results: Out of 104 eligible patients 87 (84%) participated in at least one QoL assessment. At baseline, all QLQ-C30 scales and symptoms were significantly worse than age-adjusted values for the general population. Subsequently QoL improved in general. During chemotherapy with paclitaxel, most functioning scales and symptoms worsened slightly (not significantly). However, peripheral neuropathy and chemotherapy-related side-effects increased to clinically important levels. At the end of treatment, most QoL scores were similar to those of the general population, but physical functioning and fatigue were worse. Sexual functioning and peripheral neuropathy remained problematic. Conclusion: QoL was affected mainly by the weekly paclitaxel schedule, but effects were in most cases only temporary. A dose-dense regimen using a sequential protocol may be favourable in terms of QoL.

Despite radical cytoreductive surgery and improved chemotherapy most patients with advanced ovarian cancer will suffer from tumour relapse and will die due to tumour progression (1, 2). Most trials focus only on overall and progression-free survival (3). Generally, data of haematological and non-haematological toxicities are reported without the implementation of a multidimensional approach to describe quality of life (QoL). Various trials have clearly indicated that the documentation of side effects alone is not sufficient for the interpretation of a patient’s well-being and QoL (4, 5). Thus, QoL should play a major role in the management of advanced ovarian cancer.

Several phase II trials and one phase III trial used different schedules and doses of taxanes and carboplatin in ovarian cancer with improved therapeutic index (6-8). Besides the importance of progression-free survival and overall survival rates, QoL of the different schedules are also relevant before the introduction of a specific protocol into the clinical routine.

While in recent years approximately 10% of clinical trials in oncology include QoL as one of the main outcomes (9), the literature on ovarian cancer is sparse, especially in regard to publications detailing the effects of chemotherapy on QoL (2). For dose-dense weekly paclitaxel therapy, only the

**Key Words:** Clinical phase II trial, dose-dense chemotherapy, ovarian cancer, quality of life, sequential first-line chemotherapy.
ongoing JGOG-3019 study planned to evaluate QoL as a secondary objective (8). The aim of this study was to determine, to our knowledge for the first time, the impact of the chemotherapy regimen on the patient’s life and well-being from the patient’s perspective.

Patients and Methods

This open-label multicenter phase II trial was carried out in 27 German institutions. Between July 2003 and June 2005, patients with histologically-confirmed epithelial ovarian cancer of International Federation of Gynecology and Obstetrics (FIGO) stage IA/G3-IV were enrolled. After primary cytoreductive surgery, four cycles of carboplatin (area under the curve 5) were applied, followed by 12 cycles of weekly paclitaxel at a dose of 80 mg/m² (for details, see (6)). The progression rate was defined as the primary objective of the study, while QoL, time-to-progression, response rates and toxicities were designated as secondary objectives.

QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) version 3.0 and its ovarian-specific module QLQ-OV28. These have been developed in a cross-cultural setting including Germany and Austria (10, 11).

The QLQ-C30 is a 30-item questionnaire comprising of five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial impact), and a global QoL scale summarized from two 7-point scales (overall QoL and overall general health). QLQ-C30 has been validated in several cancer patient groups including ovarian cancer patients (12). The reliability of all scales is at least satisfactory, and age and sex-specific norm values can be obtained using regression equations (13). The ovarian cancer module EORTC QLQ-OV28 was developed to assess disease and treatment-related symptoms which are not covered by the core questionnaire. The 28-item module comprises of six symptom scales (abdominal/gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side-effects, hormonal symptoms, body image, attitude to disease and treatment), and sexual functioning. All scales exhibited good psychometric properties (14). The questionnaires can be completed in a short time, of about 15 min for both (10, 14).

These QoL assessments were to be made before chemotherapy (baseline), after the four cycles of carboplatin (chemotherapy), after 12 weeks of paclitaxel (end of treatment, EOT), and at six, 12 and 24 months’ follow-up after treatment. The study was performed according to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines and approval from local review boards was gained at every centre. Clinical data, overall and progression-free survival, as well as toxicity are documented elsewhere (6).

Statistics. All scores were linearly-transformed to values of 0-100 and analyzed according to the procedures recommended by the EORTC Qol Group. Higher scores on the functional scales and the global QoL scale indicate a higher level of functioning and a better QoL. Higher scores on the symptom scales indicate a higher level of symptoms or problems. A difference of 10 points or more was considered to indicate a clinically important difference (CID) (15, 16).

The QLQ-C30 scores of the study sample were compared with expected scores representing age, standardized to the general female German population. Expected scores were calculated using regression equations reported by Schwarz and Hinz (13). For comparison of expected with observed scores, t-tests for paired samples were used.

The course of QoL was analyzed with mixed models which allow inclusion of those cases having an incomplete QoL assessment. All mixed model analyses were adjusted for age and completion because there is a clear age gradient for almost all QoL scales and symptoms (13), and patients with a complete assessment may experience a better QoL than those with incomplete assessment.

Complete assessment was defined as assessments at baseline, chemotherapy, EOT, and at least one follow-up visit. Estimated mean scores for each assessment were calculated, and comparisons of different assessments were performed using Sidak adjustment for multiple comparisons.

The predictive value of clinical factors for global QoL was analyzed with hierarchical regression models. All analyses were carried out with PASW 18 (SPSS Inc., Chicago, IL).

Results

Between July 2003 and June 2005, 105 newly-diagnosed patients were enrolled. Because one patient died after registration and prior to the start of chemotherapy, 104 patients were eligible for analysis. The median follow-up was 36 months (range=1-58 months). Overall, we received 253 evaluable questionnaires from 87 patients (84%); 23 of them had a complete assessment. Two years after EOT, the participation had decreased from 77% at baseline to less than one third (Table I).

Characteristics (age, FIGO stage, grading, ascites, residual tumour, lymph node status, death in the first year) of patients with and without any QoL assessment, as well as patients with complete and incomplete QoL-assessment were similar (data not shown). Only complete chemotherapy was more frequent in patients with QoL-assessment (84% versus 59%, p=0.041), and patients with complete assessment suffered less often from diarrhea (3% versus 16%, p=0.002) at baseline, and all of them received complete cycles of carboplatin and of paclitaxel compared to only 78% of the patients with incomplete assessment (p=0.017).

Table I. Number of evaluable quality of life assessments.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>% Eligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>80</td>
<td>76.9</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>59</td>
<td>59.6</td>
</tr>
<tr>
<td>End of therapy</td>
<td>51</td>
<td>50.5</td>
</tr>
<tr>
<td>Follow-up after 6 months</td>
<td>26</td>
<td>31.7</td>
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<tr>
<td>after 12 months</td>
<td>23</td>
<td>33.8</td>
</tr>
<tr>
<td>after 24 months</td>
<td>14</td>
<td>27.5</td>
</tr>
<tr>
<td>At least one form</td>
<td>87</td>
<td>83.7</td>
</tr>
<tr>
<td>Complete</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

The progression rate was defined as the primary objective of the study, while QoL, time-to-progression, response rates and toxicities were designated as secondary objectives.
Patients reported a low QoL at baseline. Global QoL, and almost all functional scales except cognitive functioning were scored under 60 on the 100-point scales (Table II). Sexual functioning was rated by far the lowest (Table III), e.g., the majority of patients were not sexually active throughout chemotherapy. During follow-up 6 to 24 months after EOT, only slightly more than 50% of patients were able to enjoy sex at least a little. For mean scores of the other functional scales, scores less than 60 points were not found after chemotherapy with carboplatin (chemotherapy) except for global QoL, and role functioning at EOT.

The strongest symptoms reported were burden of disease and treatment, and worrying about future health (attitude to disease and treatment), with a mean score of more than 70 points at baseline. Attitude remained problematic for many patients even two years after EOT. Fatigue and insomnia were the second strongest symptoms at baseline. Even after two years of follow-up, fatigue was scored >50 points by about 25% of the patients, while only some patients experienced some insomnia at follow-up. Body image, pain, abdominal/gastrointestinal symptoms, appetite loss, and constipation were other frequently stated symptoms. During chemotherapy with paclitaxel, peripheral neuropathy and other chemotherapy side-effects emerged as strong symptoms. Peripheral neuropathy remained for about half of the patients, and side-effects for approximately a quarter of the patients, at least a little, one or two years later.

Compared to expected values (representing age-standardized scores of the general female German population), a deterioration of QoL for the patients with ovarian cancer was observed at baseline (Table II). All domains with the exception of cognitive functioning and nearly all symptoms exhibited a CID and a statistically significant difference between the reported and the expected QoL scores. For role functioning, social functioning, physical functioning, fatigue, appetite loss,
constipation, and insomnia, the differences were of great clinical importance (e.g., a difference $>20$ points). During chemotherapy up to EOT, most functional scales and symptoms of QLQ-C30 also scored on average less than expected. In contrast, at follow-up visits most aspects of QoL were not significantly worse than expected. Only some aspects had statistically significant CIDs at different assessments.

Regression for global QoL at baseline, revealed the interval from surgery to assessment as the only significant predictor of QoL, independent of age, stage, grade, ascites, lymph node status, and residual tumour. At the subsequent assessments, the interval from surgery was no longer significantly related to global QoL, but age did emerge as a significant predictor (data not shown).

The courses of global QoL, functioning, and symptoms from baseline, during chemotherapy, and until two years after EOT are depicted in Figure 1. Estimated mean scores were derived from mixed models adjusted for age, completion of QoL assessment, and interaction of age and time. In general, QoL improved from baseline during chemotherapy until follow-up two years later, e.g., global QoL, and most functional scales increased while most symptoms decreased. During chemotherapy with paclitaxel, there was a remarkable but statistically insignificant setback of improvement. In particular, QoL was significantly improved from baseline to all other assessments for physical and role functioning, appetite loss, and also for social functioning, fatigue, and attitude to disease and treatment except assessment at EOT. Significant improvement compared to baseline for global QoL, emotional functioning, pain, abdominal/gastrointestinal symptoms, and insomnia was only observed in two or three assessments, especially at

Figure 1. Course of estimated mean scores of global QoL, functioning scales (a, b), and symptoms (c-e).
follow-up. A similar course was observed for dyspnoea and body image with a clinically important but statistically insignificant worsening during chemotherapy with paclitaxel.

Peripheral neuropathy and other chemotherapy-related side-effect followed a completely different course. These symptoms were low at baseline and also during chemotherapy with carboplatin, but emerged to a considerable extent during chemotherapy with paclitaxel. At EOT, both symptoms were significantly worse than those seen among all assessments before and after EOT. Hormonal/menopausal symptoms increased slightly but were not statistically significant. No significant differences were observed for cognitive and sexual functioning, for nausea/vomiting, constipation, diarrhea, or financial problems. The proportion of patients reporting nausea or vomiting was the highest during chemotherapy with carboplatin (19%).

In addition, there was a clear age gradient for QoL (Table IV). All functional scales except cognitive functioning and global QoL improved and most symptoms decreased significantly. Completion of QoL assessments was not associated with QoL. Only diarrhea was on average scored significantly higher by patients with incomplete assessment. Interaction effects of age and assessment were observed for role functioning and for attitude to disease and treatment. Role functioning of younger patients, e.g. those 45 years old, increased significantly during chemotherapy with carboplatin, and after EOT, showing an overall increase of more than 50 points (Figure 2). In contrast, older patients, e.g. those 70 years old, exhibited only a temporary increase in role functioning during chemotherapy with carboplatin and a stable low-level of functioning after EOT until follow-up after two years. Attitude to disease and treatment showed a reciprocal picture: for younger patients, a significant decrease of the symptoms, and for older patients, the burden and worrying remained at a high level even two years after EOT.

Discussion

The present study described the dynamic differences in QoL after radical surgery and during and after systemic chemotherapy in patients with primary ovarian cancer. The systemic chemotherapy was given in a sequential regimen with four cycles of carboplatin given every three weeks and paclitaxel given on a weekly schedule. Therefore, a separated analysis of the impact of each drug on the QoL scores was possible.

In the present study, we observed a worse QoL in patients with ovarian cancer after radical surgery and before chemotherapy, when compared to the general female population. These phenomena were also described by other groups (1, 17). It has been supposed that this is mainly due...
to incomplete recovery from radical surgery rather than from ovarian cancer itself (1, 2). This thesis was also confirmed by the results of our regression analysis for global QoL at baseline, showing that the interval from surgery to baseline assessment was the only significant predictor for global QoL.

The most frequent and important problems for patients with ovarian cancer are psychological aspects, as well as pain and loss of energy (18). Common adverse effects of chemotherapy are hair loss, peripheral neuropathy, and nausea/vomiting. Sexual dysfunction, abdominal symptoms, and hormonal or menopausal symptoms are also frequently observed (19).

In our study, patients were mainly worried about the burden of disease and treatment, and their future health, about fatigue, insomnia, pain, appetite loss, and body image. Peripheral neuropathy and other chemotherapy-related side-effects emerged to a high degree during chemotherapy with paclitaxel. Nausea or vomiting was only rated as quite a bit or very much by 19% of our participants during chemotherapy with carboplatin, and the proportion decreased to less than 10% during chemotherapy with paclitaxel. These symptoms are associated with platinum compounds and are more frequent with cisplatin than with carboplatin (1, 20). The mean score of nausea/vomiting in the carboplatin group of the Ovar3 study at EOT was similar to the mean score in our study (4).

Overall, the course of QoL of patients in our study with its sequential regimen of four cycles of carboplatin followed by 12 cycles of weekly paclitaxel appears seemed to be quite exceptional. After a rapid improvement during chemotherapy with carboplatin, QoL worsened during chemotherapy with paclitaxel, although for most aspects, this was statistically insignificant and clinically unimportant. However, peripheral neuropathy, other chemotherapy-related side-effects, and problems with body image increased to a clinically important level. After EOT, the improvement of QoL continued. Some adverse effects of paclitaxel overlap with those of carboplatin (19) and, also due to accumulation of this sequential regimen, they may increase the burden of patients with ovarian cancer. Additionally, peripheral neuropathy is related to paclitaxel itself (19). On the other hand, patients may have expected lower levels of adverse effects during chemotherapy with paclitaxel, as based on their experience of chemotherapy with carboplatin alone, where adverse effects are possibly lower than those initially feared. When the perceived adverse effects are more frequent or severe than expected, this would probably influence the appraisal of QoL negatively (20).

In general, most studies indicate a good QoL of ovarian cancer survivors (OCS) comparable to that of the general population (21-24), but in one study, OCS reported a worse global QoL than that seen in age-matched controls (25). In our study, the mean score of global QoL was comparable to that of the general female population at all follow-up assessments. But physical functioning and fatigue, as well as financial difficulties, were rated worse than the general population even two years after EOT. Low sexual functioning, worrying about future health, increased hormonal/menopausal symptoms and some patients’ persistent peripheral...
neuropathies indicate many remaining disease- or treatment-related problems. Psychological problems (body image, fear of recurrence or even death, anxiety) and physical symptoms, as well as poor sexual functioning, are also described in other studies (19, 22-24, 26, 27). Overall, it seems that OCS adapt their goals, expectations, and standards to regain a good global QoL, but they still have to face a lot of disease- and treatment-related burden. These findings support the thesis that in the health domain of life, complete adaptation does not occur, while only partial adaptation does (28).

Hormonal problems, psychological problems and the effects of radical surgery are associated with sexual dysfunction, which is a common ground in ovarian cancer (19, 23, 29). There are only few data about the influence of radical surgery and chemotherapy on the sexuality of patients with ovarian cancer. The majority of patients in the GOG152 and 172 studies were neither sexually interested nor satisfied with their sex life during the period of postoperative chemotherapy (27). In a Norwegian cross-sectional study, a lower level of sexual activity and poorer sexual functioning in OCS than in age-matched controls was observed (30). In our study, sexual functioning was also very poor; at baseline three out of four patients were not at all sexually active, and fewer than half of the patients were interested at least a little in sex after EOT. Decreased interest in sex and decreased sexual activity due to cancer was stated for about half of OCS without evidence of recurrence for at least three years after diagnosis (23). In another study, only 25% of long-term OCS stated that they were sexual active (26). Further trials are warranted to investigate the potential possibilities to address this relevant and clinically inadequately accepted topic.

Beside this relevant information from our analysis we should underline some limitations of the current study. Overall, the participation in QoL assessment during follow-up after EOT was low. Most longitudinal studies described a low compliance rate by using structured questionnaires (1, 2, 20). Drop-out may be related to negative events experienced by patients, such as treatment-related toxicities, tumour progression, or low emphasis on QoL (4, 15, 31). Based on the compliance rate, a selection bias cannot be ruled out. Nevertheless, in our analysis of QoL we did adjust for completion of QoL assessments. Study completions do not differ from non-completions in the mixed models, except for diarrhea. In other studies, differences of baseline characteristics between participants and non-participants of QoL assessments were also rarely found (1, 32).

Despite the setback during chemotherapy with paclitaxel, the improvement of QoL from baseline to EOT was similar to the improvement in the carboplatin/paclitaxel arm of the AGO-Ovar3 study (1). Mean scores of global QoL, most functional scales, and most symptoms of EORTC QLQ-C30 changed by nearly the same amount. In contrast to the data from other phase III trials using the simultaneous application of paclitaxel and carboplatin, the improvement of QoL obtained here seems to be more rapid and the patients may likely experience better QoL with the present sequential regimen. Thus, a phase III study comparing this new schedule with the conventional 3-week protocol and other dose-dense protocols comparing QoL scores and progression-free survival rate appears reasonable (33, 34).

Disclosure
The Authors declare no conflict of interest.

References


