Randomized phase III trial of 2nd line gemcitabine and paclitaxel chemotherapy in patients with advanced bladder cancer: short-term versus prolonged treatment [German Association of Urological Oncology (AUO) trial AB 20/99]


1Department of Urology, Düsseldorf University, Düsseldorf; 2Department of Urology, Bonn University, Bonn; 3Department of Urology, Charité University Berlin, Berlin; 4Department of Urology, Homburg University, Homburg; 5Department of Urology, St. Vincenz Hospital, Datteln; 6Department of Urology, Aachen University, Aachen; 7Institute of Medical Biometry, Informatics and Epidemiology, Bonn University, Bonn, Germany

Received 17 May 2010; accepted 31 May 2010

Background: The second-line chemotherapeutic treatment for metastatic urothelial cancer (UC) after failure of cisplatin-based first-line therapy needs to be improved. Based on encouraging phase II data of gemcitabine and paclitaxel (Taxol) (GP), this trial was designed to compare a short-term (arm A) versus a prolonged (arm B) second-line combination chemotherapy of GP.

Patients and methods: Of 102 randomized patients, 96 were eligible for analysis. Primary end point was overall survival (OS). Secondary end points were progression-free survival (PFS), objective response rates (ORR) and toxicity.

Results: Neither OS [arm A: 7.8 (95% CI: 4.2–11.4), arm B: 8.0 (95% CI: 4.9–11.1) months] and PFS [arm A: 4.0 (95% CI: 0–8.0), arm B: 3.1 (95% CI: 1.9–4.2) months] nor ORR (arm A: 37.5%, arm B: 41.5%) were significantly different. On prolonged treatment, more patients experienced severe anemia (arm A: 6.7% versus arm B: 26.7% grade III/IV anemia; P = 0.011). In six patients, treatment was stopped during the first cycle due to disease progression or toxicity. Two patients died due to treatment-related toxic effects.

Conclusion: Due to rapid tumor progression and toxicity at this dosage and schedule in a multicenter setting, it was not feasible to deliver a prolonged regimen. However, a high response rate of ~40% makes GP a promising second-line treatment option for patients with metastatic UC.

Key words: bladder cancer, chemotherapy, clinical trial, phase III, second-line, transitional cell carcinoma

introduction

Thirty percent of patients with urothelial cancer (UC) initially present with locally advanced (≥pT3) or metastatic disease [1]. After combination treatment of radical cystectomy and adjuvant chemotherapy, ~50% of patients with locally advanced disease and lymph node metastases will experience a disease recurrence [2]. Patients with primary metastatic disease and first-line cisplatin-based combination chemotherapy with methotrexate, vinblastine, epirubicin and cisplatin (MVAC) or gemcitabine and cisplatin (GC) will show a long-term survival of only 20% [3]. Vinflunine in combination with best supportive care (BSC), approved in the European Union in 2009 as second-line chemotherapy after failure of cisplatin-based regimens, failed to prove an overall survival (OS) advantage over BSC alone in a phase III trial [4]. Although the estimated difference in OS of 2 months was achieved in the intention-to-treat population (ITT), a significant difference in OS was only seen after removing a number of patients who were not treated according to protocol. Based on objective response rates (ORR) of single-agent paclitaxel of up to 42% in chemonaive patients [5] and modest response rates of 10% in pretreated patients [6], the combination of gemcitabine and paclitaxel (GP) was further explored in the second-line setting with ORR of up to 30% [7, 8]. The median duration of response with six cycles of GP in a 3-weekly [8] and a weekly [9] schedule was 5–10 months. Applying a GP ‘maintenance’ treatment until disease progression, a mean progression-free survival (PFS) of 6.2 months with a mean number of 6 (2–14) cycles was reached.
patients and methods

patients’ characteristics

Patients eligible for randomization had histologically confirmed metastatic UC (bladder, urethra or upper urinary tract). Patients with recurrence or progression after or during cisplatin-based first-line chemotherapy with or without radical surgery [cystectomy, nephro(ureter)ectomy] were suitable. No prior second-line chemotherapy was allowed nor was radiotherapy within 4 weeks before randomization. Bidimensionally measurable disease had to be present and life expectancy had to exceed 12 weeks. Further inclusion criteria were a Karnofsky performance score ≥60% and adequate bone marrow reserve. Patients with impaired renal (S-creatinine > 2 × upper normal limit) or cardiac function (ventricular arrhythmia, NYHA III or IV, myocardial infarct 6 months before randomization) or neurological symptoms [Common Terminology Criteria for Adverse Events (CTCAE) > I] were ineligible.

study design and statistics

This was an open-labeled randomized phase III trial. Patients were centrally randomized at Bonn University by simple random allocation. To ensure concealment of allocation, randomization was carried out after screening of eligible patients. Primary end point was OS; secondary end points were PFS, ORR and toxicity. The study was approved by all local ethics committees of participating centers. The protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

treatment and follow-up

arm A (short-term GP). A maximum of six cycles of three-weekly GP chemotherapy was administered using the following dosages:

<table>
<thead>
<tr>
<th></th>
<th>1000 mg/sqm</th>
<th>Day 1, 8 30-min infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>175 mg/sqm</td>
<td>Day 1 180-min infusion</td>
</tr>
</tbody>
</table>

The paclitaxel (Taxol) infusion was applied directly after gemcitabine. Pretreatment with 10 mg dexamethason and 2 mg clemastin intravenously (or another H1-antihistamine) before gemcitabine was recommended. Toxicity and adverse events were classified according to the CTCAE of the National Cancer Institute Version 3.0 (http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf) after every cycle. In cases of CTCAE grades III and IV hematologic toxic effects and grade IV non-hematologic toxic effects, the following cycle was delayed for a maximum of 2 weeks with a 50% dose reduction of GP dosages. A delay >2 weeks rendered the patient ‘off treatment’.

arm B (prolonged GP). The same regimen as in arm A was given until disease progression with the addition that a delay in treatment of up to 4 weeks was permitted.

definitions of recurrence and progression after second-line treatment

1 Recurrence was defined as a new, growing and bidimensionally measurable lesion after complete response after second-line treatment.
2 Progression was defined as a growing bidimensionally measurable lesion during second-line treatment.

The same definitions were applied for recurrence or progression after first-line cisplatin-based chemotherapy. A new, growing and bidimensionally measurable lesion after cystectomy and adjuvant cisplatin-based chemotherapy was also defined as recurrence after first-line therapy.

definition of tumor response and disease progression

Tumor response and disease progression were measured at every other cycle using the same imaging modality and assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) in the version of 2000 [13]. As the evaluation of tumor response was done in 2008, new RECIST criteria (version 1.1) were not applied [14].

statistical analysis

The study was designed to compare OS (primary end point) of a prolonged GP schedule with short-term GP. Based on the hypothesis of 9.1 months in OS between these two ways of treatment, the sample size calculation was carried out to achieve a power of 90% (β-error) at a level of 5% (α-error) [8–10]. Based on the sample size calculation applying the method of Dupont and Plummer, an inclusion of 104 patients was needed within 24 months [15]. The comparison of OS and PFS (time-to-event) was carried out by the two-sided log-rank test (level 5%). Comparisons of tumor responses to first- and second-line treatment were carried out by chi-square test. Cox proportional hazards model was used to examine the effects of baseline prognostic factors, i.e. duration of response to first- and second-line treatment. Statistical analysis was carried out using the Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, IL) and SAS version 9.0.
results

patients' characteristics and follow-up

From November 2001 to November 2005, 102 patients from 30 German centers (Appendix 1) were randomized to receive either short-term GP followed by BSC ($n = 51$) or prolonged GP ($n = 51$) as described in the flow chart (Figure 1). Six patients were excluded due to violation of entry criteria or lack of treatment documentation. Most recent follow-up of patients still alive was collected in February 2010.

**ITT population.** Forty-eight patients each were eligible in both treatment arms. Patients’ characteristics were well balanced (Table 1) except for the modality of first-line treatment, as a larger part of patients in arm A was treated with primary inductive chemotherapy compared with arm B.

**survival and efficacy**

OS was 7.8 (95% CI: 4.2–11.4) months in arm A and 8.0 [95% CI: 4.9–11.1] in arm B (Figure 2) ($P = 0.772$). PFS was 4.0 (95% CI: 0–8.0) months in arm A and 3.1 (95% CI: 1.9–4.2) in arm B ($P = 0.488$). In February 2010, three patients (3.1%) were still alive (arm A: 1 and arm B: 2).

In the 81 patients who had received at least one cycle of chemotherapy, response to second-line therapy was evaluated according to RECIST criteria. Regarding response parameters (complete remission, partial remission, stable disease and

*Figure 1. The consort flow chart.*
Table 1. Patients characteristics and response to first-line treatment

<table>
<thead>
<tr>
<th>Schedule A (short-term GP)</th>
<th>n = 48</th>
<th>Schedule B (prolonged GP)</th>
<th>n = 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) in years</td>
<td>63.9 (42.8–80.6)</td>
<td>65.1 (42.8–79.4)</td>
<td></td>
</tr>
<tr>
<td>Primary tumor localization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>36</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Kidney, ureter, urethra</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Combination of bladder and upper urinary tract</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Patients with hepatic and/or bone metastasis</td>
<td>20</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Patients with lymphatic metastasis only</td>
<td>12</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Median number (range) of cycles given</td>
<td>3 (0–6)</td>
<td>4 (0–17)</td>
<td></td>
</tr>
<tr>
<td>Surgery carried out before chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystectomy</td>
<td>28</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Nephroureterectomy</td>
<td>10</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>TUR-B only</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Others (e.g. tumor biopsy, partial resection)</td>
<td>4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Modality of first-line treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant after surgery</td>
<td>17</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Primary inductive chemotherapy</td>
<td>30</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GC</td>
<td>29</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>GC/paclitaxel</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>GC/amifostine</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MVAC/MVEC/MC</td>
<td>16</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

GC, gemcitabine and cisplatin; MVAC, methotrexate, vinblastine, epirubicin and cisplatin; MVEC, methotrexate, vinblatine, epirubicine and cisplatin; MC, methotrexat and cisplatin.

progressive disease), there was no significant difference between the treatment arms (Table 2). ORR was 37.5% in arm A and 41.5% in arm B (P = 0.715).

prognostic factors

response to first-line treatment. A positive correlation was found between a long duration of response to first-line treatment and the duration of response to GP. Cox-regression analysis revealed that patients who did not progress for at least 18 months after cisplatin-based first-line chemotherapy experienced best responses to second-line GP (P = 0.026, hazard ratio 0.552).

modality and regimen of first-line treatment. Patients after first-line chemotherapy in an adjuvant or neoadjuvant setting did not show any difference for both PFS and OS [3.7 (95% CI: 2.2–5.1) months, 7.8 (95% CI: 5.4–10.2) months] compared with patients after first-line chemotherapy for metastatic disease [PFS: 2.7 (95% CI: 0.2–5.2) months, P = 0.383; OS: 7.8 (95% CI: 4.4–11.3) months, P = 0.402] (Table 3).

PFS and OS in gemcitabine-pretreated patients [3.1 (95% CI: 1.7–4.4) and 8.0 (95% CI: 6.1–10.0) months] was not significantly different from patients without gemcitabine pretreatment [PFS: 4.2 (95% CI: 2.2–6.1) (P = 0.229), OS: 7.8 (95% CI: 0.9–14.8) months (P = 0.068)] (Table 3a).

site of metastases. Depending on the site of metastases, significant differences were observed for PFS, OS and ORR. In patients with lymph node metastases only, ORR was 58.3% and PFS and OS were 7.4 (95% CI: 4.6–10.2) and 13.8 (95% CI: 13.0–14.6) months, respectively (Table 3b). The differences in OS, PFS and ORR were statistically significant (P = 0.001, P = 0.002, P = 0.025).

Outcome for patients with hepatic and/or bone metastases was very unfavorable (Table 3b). ORR was only 26.7%; PFS and OS were 1.8 (95% CI: 1.0–2.7) and 5.7 (95% CI: 4.5–6.9) months compared with 5.7 (95% CI: 3.2–8.3) and 11.5 (95% CI: 7.5–15.6) months in patients without hepatic and/or bone metastases (P = 0.070, P < 0.001, P < 0.001), respectively.

Table 2. Response to study treatment according to RECIST criteria

<table>
<thead>
<tr>
<th>Schedule A (short-term GP)</th>
<th>n = 40</th>
<th>Schedule B (prolonged GP)</th>
<th>n = 41</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>5 (12.5%)</td>
<td>6 (14.6%)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>10 (25.0%)</td>
<td>11 (26.8%)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>8 (20.0%)</td>
<td>10 (24.4%)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>17 (42.5%)</td>
<td>14 (34.4%)</td>
<td></td>
</tr>
<tr>
<td>Objective response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + PR</td>
<td>15 (37.5%)</td>
<td>17 (41.5%)</td>
<td></td>
</tr>
<tr>
<td>SD + PD</td>
<td>25 (62.5%)</td>
<td>24 (58.5%)</td>
<td></td>
</tr>
</tbody>
</table>

CR, complete remission; PD, progressive disease; PR, partial remission; SD, stable disease.
Overall survival 5.7 (95% CI: 4.5–6.9) months 11.5 (95% CI: 7.5–15.6) months

Progression-free survival 1.8 (95% CI: 1.0–2.7) months 5.7 (95% CI: 3.2–8.3) months

Overall survival 13.8 (95% CI: 13.0–14.6) months 6.5 (95% CI: 5.3–7.7) months

Progression-free survival 7.4 (95% CI: 4.6–10.2) months 2.8 (95% CI: 1.7–3.9) months

Pretreatment with gemcitabine (n = 57) Pretreatment without gemcitabine (n = 39) P

Overall survival 8.0 (95% CI: 6.1–10.0) months 7.8 (95% CI: 0.9–14.8) months

Progression-free survival 4.2 (95% CI: 2.2–6.1) months 0.029

Pretreatment with gemcitabine (n = 27) Different or additional metastatic sites (n = 69) P

Overall survival 13.8 (95% CI: 13.0–14.6) months 6.5 (95% CI: 5.3–7.7) months

Progression-free survival 2.8 (95% CI: 1.7–3.9) months 0.002

Lymph node metastases only (n = 27) No hepatic and/or bone metastases (n = 62) P

Overall survival 1.8 (95% CI: 1.0–2.7) months 11.5 (95% CI: 7.5–15.6) months

Progression-free survival 5.7 (95% CI: 3.2–8.3) months <0.001

Hepatic and/or bone metastases (n = 34) No hepatic and/or bone metastases (n = 62) P

Overall survival 5.7 (95% CI: 4.5–6.9) months

Progression-free survival 3.1 (95% CI: 1.7–4.4) months 4.2 (95% CI: 2.2–6.1) months

Pretreatment without gemcitabine (n = 39) Different or additional metastatic sites (n = 69) P

Overall survival 7.8 (95% CI: 5.4–10.2) months 7.8 (95% CI: 4.4–11.3) months

Progression-free survival 3.7 (95% CI: 2.2–5.1) months 2.7 (95% CI: 0.2–5.2) months

P = 0.068

Table 3. Response to study treatment depending on (a) modality and regimen of first-line treatment and (b) metastatic site

Treatment-related toxicity

Patients with at least one dose of chemotherapy were eligible for evaluation of toxicity. A significant difference in treatment-related toxicity was only seen for anemia. Patients treated with prolonged GP developed grade III anemia in 22.2% and grade IV anemia in 4.4% compared with only 4.4% and 2.2% of patients receiving short term GP, respectively (P = 0.011). Two patients treated within arm B died due to treatment-related toxicity, one by neutropenic septicemia and the other one by pulmonary fibrosis.

discussion

Several studies investigating the combination chemotherapy of GP in patients with metastasized UC in the second-line setting report an OS of 7.0–15.8 months [7, 12, 16–20]. Trials including patients without prior chemotherapy [21] as well as trials including both pretreated and chemonaive patients [8, 22] presented equal OS rates of 11.8–14.4 months. In our trial, OS (arm A: 7.8 and arm B: 8.0 months) was lower. PFS (arm A: 4.0 months and arm B: 3.1 months) was also lower compared with previous trials (4.1–11.5 months) [7–9, 18–21].

Several reasons may explain these differences. In the trial of Li et al. [17], a higher cumulative dose of GP (3000 mg/m² gemcitabine and 330 mg/m² paclitaxel each cycle) was administered. With this regimen, an OS of 15.8 months was achieved for the price of more adverse events.

Fechner et al. [12] reported an OS of 13 months in their trial. However, only 20% of patients suffered from osseous or hepatic metastases as opposed to 35% in this trial. Also, only few patients with osseous (10%) and hepatic (7%) metastases were included in the trial of Sternberg et al. [7] (biweekly GP), who reported an OS of 14.4 months. A positive patient selection and low patient numbers (36, 30 and 41 patients in the trials of Li et al. [17], Fechner et al. [12] and Sternberg et al. [7], respectively) may also have contributed to the relatively high OS reported in these publications.

Of 96 eligible patients in this trial, 6 had to stop treatment during the first cycle because of toxicity; 4 patients even died before chemotherapy was initiated. This may be due to poor prognosis along with a reduced general condition of this patient population. This problem was observed in other trials as well. For example, Fechner et al. [12] reported a drop-out rate of 10% due to adverse events during the first cycle. In the trial of Li et al. [12], 3 of 36 patients needed to stop treatment during the first cycle due to toxicity and rapid tumor progression. Recently, poor prognosis of this population was demonstrated by Bellmunt et al. [4] in a phase III second-line protocol (Vinflunine versus. BSC). Median survival was unfavorable with only 4.3 months for the BSC group.

Considering the patients’ poor prognosis, it is not surprising that prolonged treatment with GP, except for some rare cases, was not feasible. The median number of cycles that could be delivered in both treatment arms did not differ at all (arm A: 3 cycles and arm B: 4 cycles). These numbers compare well with several other reports [16–18].

description of prognostic factors

Since both groups of patients did not differ in patients’ characteristics (poor prognosis), treatment modalities (number of cycles administered) and outcome (OS, PFS and ORR), all patients were analyzed for prognostic factors of treatment response.

lymph node metastases only. Compared with patients presenting with metastases at additional sites, OS, PFS and ORR were better in patients with lymph node metastases only. PFS and OS in these patients (n = 27) were 7.4 months and 13.8 months, respectively, as opposed to patients with additional metastases or other metastatic sites (2.8 and 6.5 months). ORR was 58.3% (lymph node metastases only) compared with 31.6% (additional/other metastatic sites).

A better outcome of patients with lymph node metastases only receiving GP second-line treatment was already reported in prior studies. Fechner et al. [12] were able to show an OS of 15 months in patients with lymph node metastases, whereas patients with bone and liver metastases only had an OS of 5 and 4 months, respectively. Sternberg et al. [7] showed ORR of 60%–71% in patients with lymph node metastases at different sites compared with 38% (lung) and 33% (liver). High response rates for patients with lymph node metastases (93% and 75%) were also reported in two other trials leading to a significant advantage in OS [17, 19].
bone and hepatic metastases. Patients with hepatic and bone metastases \( (n = 34) \) showed a median PFS and an OS of only 1.8 and 5.7 months, respectively. ORR (26.7%) was also worse in this subgroup. This compares well to the OS of these patients in other trials with 4–5 months \( [7, 12] \) and does not differ from the OS with BSC in the study of Bellmunt et al. \[4\]. In the trial of Kanai et al. \[19\], only one of nine patients with bone metastases experienced a response. With regard to this outcome, it is a reasonable question whether such patients may have a greater benefit from BSC instead of second-line chemotherapy.

**response to first-line treatment.** Patients with a duration of response to platinum-based first-line treatment ≥18 months seemed to benefit most from a second-line treatment with GP. Response to second-line treatment was independent of progression after adjuvant or primary inductive chemotherapy indicating that patients with progression after cystectomy and adjuvant treatment do not a priori present a more favorable subgroup. Gemcitabine-naïve patients did not show a better response in terms of OS and PFS compared with gemcitabine-pretreated patients.

Concerning the predictive power of the response to first-line treatment, only limited data are published in the literature. Applying a GP regimen as second-line treatment, Suyama et al. \[20\] reported a median survival of 7.2 months in patients with early relapse (<3 cycles of first-line chemotherapy) compared with 12.6 months in patients with good response to first-line treatment. Due to the few patients enrolled in this study, the difference was not significant. Kanai et al. \[19\] were able to show a positive correlation between response to first-line treatment with MVAC and second-line treatment with GP, though in this trial, only 20 patients were included. Testing the efficacy of vinflunine as second-line treatment, Culine et al. \[23\] achieved disease control in 75% of patients with a response duration of >12 months compared with 58%, if tumor progression occurred within 4 months.

Sparse information is available also concerning the impact of the modality of first-line on the efficacy of second-line treatment. Fechner et al. \[12\] report, although not statistically significant, a favorable PFS and OS for patients after adjuvant (8.5 and 15.0 months, respectively) compared with primary inductive chemotherapy (8.0 and 10.4 months). Similar results were presented by Kouno et al. \[24\]. In this trial applying paclitaxel and carboplatin in the second-line setting, OS was 12.4 months in patients treated adjuvantly compared with 7.9 months in patients treated for metastatic disease. Sternberg et al. \[7\] report a significant difference in OS between patients with prior adjuvant chemotherapy (12 months) or treatment for metastatic disease (8 months) receiving biweekly GP as second-line treatment. In contrast to these results, other study groups were not able to show any difference in efficacy of second-line treatment comparing adjuvant/neoadjuvantly treated patients to patients treated for primary metastatic disease \[20, 25\]. For example, evaluating paclitaxel in second-line treatment of UC, Sweeney et al. \[25\] achieved similar response rates (27.8% versus 27.6%) as well as a similar OS (10.0 versus 9.2 months) in patients with prior adjuvant/neoadjuvant treatment and treatment for metastatic disease.

**strengths and weaknesses**

The strength of this trial is the relatively large patient cohort and the clear message that prolonged second-line chemotherapy is not feasible. In addition, patients with adjuvant chemotherapy did not differ in terms of response from patients with progression of metastatic lesions after first-line chemotherapy. However, a more homogeneous population would have provided clearer results in terms of prognostic factors for response. Based on previously published phase II data, the expected difference in OS in retrospect was overoptimistic. Another weakness of the trial is the large number of centers who included less than two patients; fewer centers would have enlarged the patient population available for response and toxicity analysis.

**conclusions**

In this randomized phase III trial, it was not possible to demonstrate a superior OS and PFS of prolonged compared with short-term GP in second-line treatment after failure to cisplatin-based chemotherapy. A subgroup of patients with favorable prognostic factors, including lymph node metastases only and a long-lasting duration of response to first-line treatment, may benefit most from second-line therapy with GP. Neither modality (adjuvant/neoadjuvant versus primary inductive) nor regimen (pretreatment with or without gemcitabine) had an impact on response and efficacy of second-line GP. With a median number of four chemotherapy cycles, prolonged treatment does not seem feasible.

**funding**

Lilly Oncology Inc.; Bristol Meyers Squibb Inc.

**acknowledgements**

The trial design was approved by the German Cancer Society. Randomized Trial Registration Number: German Cancer Society (Deutsche Krebsgesellschaft) 01-09 (Studien mit Gütesiegel 2002, www.krebsgesellschaft.de). Parts of the data have been presented at the 2008 Annual Meeting of the American Society of Clinical Oncology in Chicago.

**disclosure**

The authors declare no conflict of interest.

**references**


appendix 1

Participating Centers (number of accrued patients in brackets)

Bonn University (20), Klinikum Kassel GmbH (18), Charité Berlin, CBF (8), Homburg University (6), Vincenz Hospital Datteln (5), Cologne University (5), Klinikum Langen/Debstedt (4), St. Josefs Hospital Krefeld (4), Hannover University MHH (3), Tübingen University (3), St. Josefs Hospital Dortmund (2), Klinikum Bad Hersfeld (2), Krankenhaus Nordwest Frankfurt (2), Marburg University (2), Klinikum Offenbach (2), Rostock University (2), Klinikum Bayreuth (1), Klinikum Berlin-Neukölln (1), Klinikum Bruchsal (1), Klinikum Demmin (1), Diakonissenkrankenhaus Dresden (1), Klinikum Golzheim Düsseldorf (1), Städtisches Klinikum Fulda (1), St. Elisabeth-Krankenhaus Köln (1), St. Elisabeth-Krankenhaus Leipzig (1), Klinikum Ludwigsfeld (1), St. Elisabeth Hospital Neuwied (1), Diakonie Krankenhaus Schwäbisch-Hall (1), Urolog. Praxis, Stuttgart (1), Klinikum Velbert (1).