Capecitabine plus oxaliplatin (CapOx) versus capecitabine plus gemcitabine (CapGem) versus gemcitabine plus oxaliplatin (mGemOx): final results of a multicenter randomized phase II trial in advanced pancreatic cancer


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Received 23 July 2007; revised 24 August 2007; accepted 27 August 2007

Background: To compare the efficacy and safety of three different chemotherapy doublets in the treatment of advanced pancreatic cancer (PC).

Patients and methods: At total of 190 patients were randomly assigned to receive capecitabine 1000 mg/m² twice daily on days 1–14 plus oxaliplatin 130 mg/m² on day 1 (CapOx), capecitabine 825 mg/m² twice daily on days 1–14 plus gemcitabine 1000 mg/m² on days 1 and 8 (CapGem) or gemcitabine 1000 mg/m² on days 1 and 8 plus oxaliplatin 130 mg/m² on day 8 (mGemOx). Treatment cycles were repeated every three weeks. The primary end point was progression-free survival (PFS) rate at 3 months; secondary end points included objective response rate, carbohydrate antigen 19-9 response, clinical benefit response, overall survival and toxicity.

Results: The PFS rate after 3 months was 51% in the CapOx arm, 64% in the CapGem arm and 60% in the mGemOx arm. Median PFS was estimated with 4.2 months, 5.7 months and 3.9 months, respectively (P = 0.67). Corresponding median survival times were: 8.1 months (CapOx), 9.0 months (CapGem) and 6.9 months (mGemOx) (P = 0.56). Grade 3/4 hematological toxicities were more frequent in the two Gem-containing arms; grade 3/4 non-hematological toxicity rates did not exceed 15% in any arm.

Conclusion: CapOx, CapGem and mGemOx have similar clinical efficacy in advanced PC. Each regimen has a distinct but manageable tolerability profile.

Key words: capecitabine, chemotherapy, gemcitabine, pancreatic cancer, oxaliplatin

Introduction

In 2006, an estimated 33 730 new cases of pancreatic cancer (PC) were diagnosed in USA, and PC is currently the fourth most frequent cause of death from cancer [1]. Despite some progress in chemotherapeutic treatment since the introduction of the nucleoside analog gemcitabine, the prognosis of patients with advanced PC remains very poor [2]. The reported median survival time for patients treated with single-agent gemcitabine in phase III trials ranged from 4.9 to 7.2 months [3, 4]. In the past decade, >15 randomized phase III trials investigated the role of gemcitabine-based combination chemotherapy in advanced PC. In order to improve therapeutic efficacy, standard gemcitabine treatment was mainly combined with antimetabolites, platinum analogs or topoisomerase inhibitors [4]. The most promising results were obtained when gemcitabine was combined with the oral fluoropyrimidine capecitabine or with a platinum compound like cisplatin or oxaliplatin [5–8]. However, preliminary results of only one of these trials showed a statistically significant survival benefit for
chemotherapy with gemcitabine plus capecitabine compared with single-agent gemcitabine [8]. Also the combination of gemcitabine with the epidermal growth factor receptor tyrosinekinase inhibitor erlotinib showed a statistically significant survival benefit for the combination regimen [9]. Thus, the optimal combination chemotherapy regimen in advanced PC still remains to be defined.

The purpose of this randomized phase II trial was to investigate and exploratively compare the three chemotherapy doublets capecitabine plus oxaliplatin (CapOx), capecitabine plus gemcitabine (CapGem) and a modified gemcitabine plus oxaliplatin (mGemOx) regimen in terms of efficacy and safety in the treatment of patients with advanced PC. Results from phase II and phase III studies evaluating combination chemotherapy with CapGem and GemOx have been reported previously [6–8, 10, 11]. However, the mGemOx regimen used in our trial is different than the one previously reported by Louvet and co-workers [6]: specifically, oxaliplatin is applied on day 8 of a 3-week cycle (instead of day 2 of a 2-week cycle) and gemcitabine is given as a 30-min infusion (not as a fixed-dose rate infusion (FDR) of 10 mg/m²/min). This trial is the first randomized comparison of CapOx, CapGem and the mGemOx. To date, there are neither trials comparing the two combinations of mGemOx and CapGem with each other, nor studies that have evaluated the role of a CapOx regimen in the first-line treatment of advanced PC [12, 13].

patients and methods

patient population

Patients between the age of 18 and 75 years with a histologically confirmed diagnosis of locally advanced (stage III) or metastatic (stage IV) PC not amenable to treatment with curative intent (either by surgery or radiotherapy) were included in this trial. No prior chemotherapy and no prior radiation therapy were allowed. Major eligibility criteria included a bidimensionally measurable lesion according to the World Health Organization (WHO) criteria, a Karnofsky performance status (KPS) of ≥60%, a life expectancy of at least 3 months and adequate bone marrow, hepatic and renal function. Patients with preexisting peripheral neuropathy, known dihydropyrimidine dehydrogenase deficiency or any other malignancy within the past 5 years (except curatively treated basal cell skin cancer or carcinoma in situ of the cervix uteri) were excluded. Pregnant or breast-feeding women and patients unable to use an approved contraceptive method during study treatment were also excluded. The study had approval of the ethical committees in all participating German centers and each patient gave written informed consent before any study-specific procedure. This study was conducted according to the Declaration of Helsinki.

study design and treatment

This was an open-label, multicenter, three-arm randomized phase II trial. Patients were stratified according to disease stage (locally advanced versus metastatic) and performance status (KPS > 70% versus KPS ≤ 70%). The primary study end point was progression-free survival (PFS) after 3 months; secondary end points were overall survival (OS), objective response rate (ORR), carbohydrate antigen 19–9 (CA 19–9) tumor marker response, clinical benefit response (CBR) and toxicity.

In the CapOx arm, patients received capecitabine (Xeloda®; Hoffmann-La Roche, Grenzach-Wyhlen, Germany) 1000 mg/m² twice daily po on days 1–14 followed by a treatment-free interval of seven days and oxaliplatin (Eloxatin®; Sanofi-Aventis, Frankfurt/Main, Germany) 130 mg/m² i.v. over 120 min on day 1. The CapGem arm, treatment consisted of capecitabine 825 mg/m² twice daily po, oxaliplatin 130 mg/m² i.v. over 120 min on day 1 and 8. Patients in the mGemOx arm were treated with gemcitabine 1000 mg/m² i.v. over 30 min on day 1 and 8 and oxaliplatin 130 mg/m² i.v. over 120 min on day 8. In all three treatment arms, courses were repeated every 3 weeks until disease progression or unacceptable toxicity. If necessary, protocol-defined dose reductions were carried out according to clinical and laboratory parameters. Supportive treatment (e.g. antiemetic therapy) was administered according to local standards of the participating centers.

efficacy and safety evaluation

Physical examination including body weight, KPS, vital signs and blood analysis (hematology, serum chemistry and CA 19-9) were carried out on day 1 of each cycle. ORR was evaluated according to the WHO criteria every two cycles (every 6 weeks) using ultrasound, computed tomography and magnetic resonance imaging scans. CBR was defined according to the criteria previously published by Burris et al. [2]: changes in pain (pain intensity and analgesic consumption), KPS and body weight were used to classify patients as responders or nonresponders.

Tumor marker response was classified based on a CA 19-9 decline of ≥20% and ≥50% after 6 weeks of chemotherapy, respectively [14]. All patients with at least one CA 19-9 measurement at baseline and after two cycles of treatment were included in this analysis. If no CA 19-9 measurement was carried out on day 1 of cycle 3, the CA 19-9 value from day 1 of cycle 4 was used—if available—for determination of CA 19-9 response.

For the determination of PFS and OS, all patients randomized according to the protocol inclusion and exclusion criteria were included. Toxicity analyses were carried out for each patient who received at least one dose of the study drugs according to the protocol. Toxicity was assessed at the beginning of each cycle and classified according to the National Cancer Institute—Common Toxicity Criteria, version 2.0.

baseline KPS as a prognostic factor

Based on recent observations showing an important prognostic role of KPS for patients with advanced PC receiving systemic chemotherapy [5, 15], a post hoc subgroup analysis was carried out. Patients were separated into groups with a good (KPS ≥ 90%) and a poor baseline performance status (KPS ≤ 80%), and the subgroups were analyzed for PFS and OS.

statistical analyses

This trial was designed as a three-arm randomized phase II study. This design was chosen in order to define the most promising regimen, which could be further evaluated in a phase III setting or serve as a platform for future trials incorporating new (e.g. targeted) agents [16]. The primary outcome measure of this study was the PFS rate after 3 months. PFS was defined as the time from random assignment until tumor progression or death. Assuming a PFS rate of 50% after 3 months following treatment with single-agent gemcitabine, a similar finding in this study would be considered as futile. In contrast, we assumed that an experimental combination regimen which achieved a PFS rate of 70% after 3 months would be regarded as a promising candidate for further evaluation. Based on a power of 90% and a type I error rate of 5%, a total population of 150 patients (50 in each arm) was required, with some over recruitment prospectively planned in order to allow for dropouts. All time-to-event curves for PFS and OS were estimated according to the Kaplan–Meier method, and differences between groups were analyzed using the log-rank test [17]. Fisher’s exact test was applied for evaluating...
differences in ORR and CBR. For comparing toxicity rates, the Mantel–Haenszel test was used. Due to the phase II design of the trial, all statistical tests were of an explorative nature, with all given P values being two-sided.

**results**

**patient characteristics**

From July 2002 to May 2004, 190 patients from 44 German centers were enrolled in this study. A Consolidated Standards of Reporting Trials diagram is shown in Figure 1. The database was closed for final analysis in August 2006. Baseline patient characteristics are summarized in Table 1. Relevant patient characteristics were well-balanced between the treatment arms, especially with regard to known prognostic factors like stage of disease and performance status. The majority of patients (87%) had a KPS of >70%, and 82% of all patients had metastatic disease.

**treatment**

A total of 1035 cycles of chemotherapy were administered in this study (CapOx 296 cycles, CapGem 443 cycles, mGemOx 296 cycles). Patients in the CapOx arm received a median of three cycles (range, 1–21), patients in the CapGem arm six cycles (range, 1–25) and patients treated with mGemOx five cycles (range, 1–14). Treatment delays occurred in 19% of all cycles in the CapOx arm, in 23% of cycles in the CapGem arm and in 27% of cycles in the mGemOx arm. The main reasons for treatment postponement are shown in Table 2. In 25% of all treatment cycles, doses had to be reduced mainly due to treatment-related toxicity. Whereas hematological toxicity was the main reason for dose reduction in the two gemcitabine-containing treatment arms (84% CapGem, 67% mGemOx, 10% CapOx), non-hematological toxicities were the main causes for dose reduction in the CapOx arm (Table 2).

The three main reasons for discontinuation of study treatment were tumor progression (51%), treatment-related toxic effects (19%) and patient refusal (14%). In the mGemOx arm, 26% of patients discontinued treatment due to toxic effects, in the CapOx arm 20% and in the CapGem arm 13%.

**efficacy results**

**response by imaging criteria, CA 19-9 and CBR.** Detailed results for ORR, CA 19-9 tumor marker response and CBR are summarized in Table 3. No complete responses were observed. Partial responses (defined by WHO criteria) were seen in 13% of patients in the two oxaliplatin-containing treatment arms and in 25% of patients in the CapGem arm (P = 0.13).

One hundred and thirty-seven patients were assessable for CBR (CapOx 42, CapGem 52 and mGemOx 43). Based on an intention-to-treat analysis, 11% of patients in the CapOx arm were classified as responders, compared with 23% of patients in the CapGem arm and 30% of patients in the mGemOx arm (Table 3).

**survival results. pfs:** At the time of final analysis, 175 of 188 patients (93%) had an event relevant for determination of PFS. Median PFS for all patients was 4.3 months [95% confidence interval (CI) 3.6–5.1], and after 3 months 60% of patients (95% CI 54–68) were alive without tumor progression. PFS results are summarized in Table 4; the corresponding Kaplan–Meier plot for PFS is shown in Figure 2A. PFS rate after 3 months, the primary study end point, was 51% in the CapOx arm, 64% in the CapGem arm and 60% in the mGemOx arm. Median PFS was 4.2 months in the CapOx arm, 5.7 months in the CapGem arm and 3.9 months in the mGemOx arm (P = 0.67).

Exploratory analysis of possible advantages regarding PFS between the CapGem and CapOx arms (P = 0.42) and between the CapGem and mGemOx arms (P = 0.47) showed no significant differences.

**os:** At the time of final analysis, 161 of 188 patients (86%) evaluated for OS had died. Median survival of all patients was 8.1 months (95% CI 7.3–9.3). Detailed results for OS are

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**Figure 1.** Consolidated Standards of Reporting Trials diagram. Cap, capecitabine; Ox, oxaliplatin; Gem, gemcitabine; ORR, overall response rate; PFS, progression-free survival; OS, overall survival; SAE, severe adverse event.
summarized in Table 4 and Figure 2B. Median OS for patients receiving CapOx was 8.1 months, for CapGem 9.0 months and for patients treated with mGemOx 6.9 months ($P = 0.56$). The corresponding 1-year OS rates were 29%, 33% and 22%, respectively. Survival comparisons in pairs resulted in no significant differences for CapGem versus CapOx ($P = 0.82$), CapGem versus mGemOx ($P = 0.29$) and CapOx versus mGemOx ($P = 0.46$).
Table 3. Efficacy results: objective response rates, CA 19-9 tumor marker response and CBR (n = 188)

<table>
<thead>
<tr>
<th>Response</th>
<th>CapOx (n = 61)</th>
<th>CapGem (n = 64)</th>
<th>mGemOx (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Overall response ratea</td>
<td>8</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>95% CI</td>
<td>6–24</td>
<td></td>
<td>15–37</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>22</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>Disease control rateb</td>
<td>30</td>
<td>49</td>
<td>41</td>
</tr>
<tr>
<td>95% CI</td>
<td>36–62</td>
<td></td>
<td>51–76</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>14</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Not assessable</td>
<td>17</td>
<td>28</td>
<td>7</td>
</tr>
<tr>
<td>CA 19-9 decline &gt;20%</td>
<td>15</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>CA 19-9 decline &gt;50%</td>
<td>12</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>CBRc</td>
<td>7</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>95% CI</td>
<td>5–22</td>
<td></td>
<td>14–36</td>
</tr>
</tbody>
</table>

For the determination of CA 19-9 response, data from 95 patients were available (CapOx 27, CapGem 38, mGemOx 30).

Disease control rate = rate of complete response + partial response + stable disease.

aGlobal P value = 0.13.

bGlobal P value = 0.26.

cGlobal P value = 0.023.

CA 19-9, carbohydrate antigen 19-9; CBR, clinical benefit response; Cap, Capecitabine; Ox, Oxaliplatin; Gem, Gemcitabine; CI, confidence interval.

Table 4. Efficacy results: PFS and OS (n = 188)

<table>
<thead>
<tr>
<th>Survival end point</th>
<th>CapOx (n = 61)</th>
<th>CapGem (n = 64)</th>
<th>mGemOx (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months4</td>
<td>4.2</td>
<td>5.7</td>
<td>3.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>2.3–5.6</td>
<td>3.6–6.3</td>
<td>3.0–5.4</td>
</tr>
<tr>
<td>3-month PFS rate, %</td>
<td>51</td>
<td>64</td>
<td>60</td>
</tr>
<tr>
<td>95% CI</td>
<td>40–65</td>
<td>53–77</td>
<td>49–74</td>
</tr>
<tr>
<td>1-year PFS rate, %</td>
<td>8</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>95% CI</td>
<td>3–19</td>
<td>7–24</td>
<td>4–21</td>
</tr>
<tr>
<td>Median OS, monthsb</td>
<td>8.1</td>
<td>9.0</td>
<td>6.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>6.7–10.2</td>
<td>7.7–11.5</td>
<td>5.1–9.0</td>
</tr>
<tr>
<td>1-year OS rate, %</td>
<td>29</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>95% CI</td>
<td>19–44</td>
<td>23–47</td>
<td>13–38</td>
</tr>
</tbody>
</table>

aGlobal P value = 0.67.

bGlobal P value = 0.56.

PFS, progression-free survival; OS, overall survival; Cap, capecitabine; Ox, oxaliplatin; Gem, gemcitabine; CI, confidence interval.

Discussion

This phase II study is the first prospective clinical trial that has compared three different chemotherapy doublets in the
treatment of advanced PC. The benefit of combining gemcitabine with a second cytotoxic agent still remains controversial in this disease: phase III trials evaluating the addition of a platinum compound to standard gemcitabine have shown a significant increase in ORR and PFS, but not in OS [5, 6]. Only a preliminary analysis of the trial by Cunningham and co-workers [8] showed a significant increase in median OS for the combination of GemCap when compared to single-agent gemcitabine (7.4 versus 6.0 months, \( P = 0.026 \)). In this study, a 4-week regimen for capcitabine was used: capcitabine was given at a total dose of 1660 mg/m\(^2\)/d for 21 days every 4 weeks. In contrast, our trial (capcitabine 1650 mg/m\(^2\)/d for 2 weeks out of three) as well as the phase III study conducted by Herrmann and co-workers [7] (capcitabine 1300 mg/m\(^2\)/d for 2 weeks out of three) used a 3-week regimen. However, the Herrmann study failed to demonstrate a survival benefit for the combination regimen (8.4 versus 7.2 months, \( P = 0.234 \)) [7].

The results from a previous phase III trial showed an encouraging median OS for the GemOx regimen (9 months) compared with single-agent gemcitabine (7.1 months, \( P = 0.13 \)) [6]. Based on these data, the Eastern Cooperative Oncology Group trial E6201 was designed as a three-arm randomized phase III study to answer two questions: first, the effect of administering gemcitabine by a FDR (1500 mg/m\(^2\) >150 min [18, 19]) instead of a standard 30-min infusion of 1000 mg/m\(^2\) (Burris regimen); and second, the contribution of oxaliplatin when added to FDR gemcitabine (Louvet regimen) [20]. Preliminary results demonstrated short survival times: median OS in the standard arm with gemcitabine applied as a 30-min infusion was 4.9 months, and both investigational arms showed an increase in OS of about 1 month when single-agent gemcitabine was given as a FDR infusion or when oxaliplatin was added to FDR gemcitabine [20]. In our trial, a median survival time of 6.9 months was achieved with a modified mGemOx regimen.

Possible explanations for varying results between different clinical trials are difficult to assess: reasons may be found, for example, in different drug schedules (e.g. gemcitabine 30-min infusion versus FDR infusion; capcitabine as a 3-week versus 4-week regimen) as well as in differences between patient populations or inter-study variations in second-line treatment, respectively. Even if a comparison of survival results between different randomized trials is rejected as not appropriate, there is at least increasing evidence for an important role of a CapGem regimen in the treatment of advanced PC: median OS for the GemCap combination in the Cunningham trial was 7.4 months, and 8.4 months in the phase III study conducted by Herrmann and co-workers, respectively [7, 8]. However, the Swiss trial did not show statistical superiority for GemCap compared with gemcitabine alone, possibly also due to an underpowered design of the study. Furthermore, the median OS in the control arm (7.2 months) is the longest survival for single-agent gemcitabine ever reported from a phase III trial. The results from our study, with an estimated median PFS of 5.7 months and an OS of 9.0 months for the CapGem regimen, further support these data. Taking these results together—with the known limitations described above—one may possibly favor the CapGem regimen as a platform for further clinical studies (e.g. incorporating targeted agents) in advanced PC. However, based on the statistical study end points, also in our trial none of the experimental regimens met the predefined primary end point (PFS rate after 3 months ≥70%).

This is the second randomized trial in advanced PC to incorporate a gemcitabine-free combination chemotherapy arm (CapOx) [21]. CapOx has been studied widely in patients with colorectal cancer and yielded encouraging results, regarding both therapeutic efficacy and toxicity [12, 13]. Based on our data, the efficacy of the CapOx regimen in the treatment of advanced PC seems to be similar to gemcitabine-containing combination regimens. However, the toxicity profile is different with significantly fewer hematological adverse events. Major side-effects of this combination are non-hematological, with neuropathy and hand-foot syndrome being the main reasons for dose reductions (Table 2). Thus, further studies with CapOx in patients with PC are warranted. As there is still an unclear role of second-line chemotherapy after gemcitabine failure in PC [22], clinical studies evaluating CapOx in this setting may be a promising approach [23].

In conclusion, the final results of this randomized trial demonstrate that CapOx, CapGem and the modified mGemOx have similar clinical efficacy according to both primary and secondary study end points. Significant differences were
observed in toxicity profiles, but all regimens were tolerated well and side-effects were manageable. Future trials of combination chemotherapy in advanced PC should focus on defined subgroups of patients, e.g. those with metastatic disease and a good performance status [5, 7, 15, 24].

**funding**

Hoffmann-La Roche, Germany; Sanofi-Aventis, Germany.

**acknowledgements**

The authors wish to thank all patients and their families, nurses, study coordinators and investigators for their active participation in this study.


**appendix**

The following study centers and persons participated in this trial:

- Medizinische Klinik und Poliklinik III, Klinikum Grosshadern, Ludwig-Maximilians-Universität München (Dr S. Boeck, Dr Golf, Prof. V. Heinemann);
- I. Medizinische Klinik und Poliklinik, Universität Mainz (Prof. Dr Hoeherler);
- Onkologische Schwerpunktpraxis, Bad Soden (PD Dr Seipel);
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- Medizinische Klinik I, Universitätsklinikum Erlangen (PD Dr Wein);
- III. Medizinische Klinik, Medizinische Fakultät Mannheim, Universität Heidelberg (Prof. Hochhaus);
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- Klinik für Hämatologie/Onkologie, Städtisches Klinikum Magdeburg (Dr Kettner);
- Onkologische Schwerpunktpraxis, Kronach (Dr Stauch, Dr Schelb);
- Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München (PD Dr Lordick);
- Innere Medizin I, Johanner Krankenhaus Bonn (Prof. Ko);
- Medizinische Klinik II, Universitätsklinikum Freiburg (Prof. Geissler);
- Medizinische Klinik II, Universitätsklinikum Leipzig (Dr Schoppmeyer);
- Onkologische Schwerpunktpraxis, Darmstadt (Dr Kojouharoff);
- Onkologische Schwerpunktpraxis, Augsburg (Dr Brudler, Dr Heinrich);
- II. Medizinische Klinik, Städtisches Klinikum Karlsruhe (Dr Takkin);
- Medizinische Klinik Mitte, Klinikum Dortmund (Prof. Heike);
- Onkologische Schwerpunktpraxis, Rüsselsheim (Dr Baldus, Dr Wurmell);
- Medizinische Klinik II, Klinikum Memmingen (PD Dr Wein);
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- Innere Klinik I, Karl-Olga Krankenhaus Stuttgart (Dr Hämmerle);
- Medizinische Klinik, Städtklinik Baden-Baden (Dr Staiger);
- Klinik für Chirurgie, Universitätsklinikum Giessen (Dr Rose);
- Onkologische Schwerpunktpraxis, Erding (Dr Schmidkonz);
- Onkologische Schwerpunktpraxis, Magdeburg (Dr Krönig, Dr Muller, Dr Uhle);
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- Thüringenklinik Saalfeld (Dr Fenchel);
- Medizinische Klinik II, St Johannes Hospital Dortmund (Dr Hagen);
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- Innere Medizin, St Vinzenz und Elisabeth Hospital Mainz (Dr Mühle);
- Innere Medizin I, Universitätsklinikum des Saarlandes, Homburg/Saar (Dr Kranzhofer);
- Onkologische Schwerpunktpraxis, München (Dr Abenhardt);
- Innere Abteilung, Kreiskrankenhaus Tirschenreuth (Dr Dertinger).

### Table 5. Toxicity results according to NCI–CTC, version 2.0 (maximum per patient)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CapOx ($n = 58$) grade</th>
<th>CapGem ($n = 63$) grade</th>
<th>mGemOx ($n = 60$) grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1–2</td>
<td>3–4</td>
<td>1–2</td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>19</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Anemia</td>
<td>39</td>
<td>2</td>
<td>54</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>37</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>31</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>67</td>
<td>9</td>
<td>66</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40</td>
<td>3</td>
<td>29</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Mucositis</td>
<td>11</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Alopecia</td>
<td>17</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Infection</td>
<td>14</td>
<td>2</td>
<td>24</td>
</tr>
</tbody>
</table>

NCI–CTC, National Cancer Institute–Common Toxicity Criteria; Cap, capecitabine; Ox, oxaliplatin; Gem, gemcitabine.


