Dose-dense therapy is of benefit in primary treatment of ovarian cancer: contra

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Several studies in the past have tried to improve the prognosis of ovarian cancer by increasing the dose intensity of platinum. Only 2 out of 12 randomized studies showed survival benefit at the cost of significant long-term toxicity. Dose-dense induction therapy with combined weekly paclitaxel (at a dose of 90 mg/m²) and weekly carboplatin [at an area under the curve (AUC) of 4 mg/ml/min] followed by 3-weekly paclitaxel/carboplatin was very effective in platinum-resistant patients (response 58%, progression-free survival 10 months). In first-line, however, no survival benefit was found with the same dose-dense weekly paclitaxel/carboplatin regimen over standard-dosed 3-weekly paclitaxel/carboplatin in a randomized study.

Very recently, the Japanese Gynecologic Oncology Group (JGOG) study no. 3016, randomizing patients in first-line between dose-dense weekly paclitaxel 80 mg/m² plus 3-weekly carboplatin AUC 6 and 3-weekly paclitaxel/carboplatin, showed a significant increase in progression-free survival (median 28 versus 17.2 months in the control arm; hazard ratio for progression, 0.71; 95% confidence interval, 0.58–0.88; \( P = 0.0015 \)). The 3-year overall survival was 72% versus 65% (\( P = 0.03 \)), respectively. The hematologic toxicity was substantial in both arms and substantially higher than observed with the weekly paclitaxel/carboplatin induction regimen. Many patients had treatment delays, dose reductions and stopped treatment prematurely.

The JGOG 3016 study is the only dose-dense study with such a significant survival benefit. It is also the only dose-intensity study performed in Asian patients. Genotypes and phenotypes are thought to represent important determinants of drug efficacy in ovarian cancer. Therefore, confirmatory studies with this JGOG regimen together with translational research are needed in both Caucasian and Asian patients.

Key words: dose density, dose intensity, first-line therapy, epithelial ovarian cancer, weekly paclitaxel, weekly platinum

introduction

Cytoreductive surgery, upfront or after neoadjuvant chemotherapy, and six cycles of 3-weekly paclitaxel/carboplatin is the standard treatment for advanced epithelial ovarian cancer (EOC). With this standard treatment the median progression-free survival (PFS) varies between 16 and 21 months and the median overall survival (OS) between 32 and 57 months [1–8]. The addition of a third cytotoxic agent to standard 3-weekly paclitaxel/carboplatin, in triplets or in sequential doublets, did not improve OS or PFS [9–11]. Although the response rate to standard paclitaxel/carboplatin is high, most patients still experience a recurrence and will finally die due to the disease. New strategies are needed to improve the outcome in advanced-stage ovarian cancer. In a retrospective analysis, Levin and Hryniuk [12] showed a positive relationship between clinical outcome and the dose intensity of standard first-line therapy. Several prospective randomized studies have investigated the potential benefit of increased platinum dose intensity on the outcome of advanced ovarian cancer.

platinum dose intensity in first-line therapy

increased platinum dose intensity per cycle

Several studies have investigated the effect of an increased dose intensity of cisplatin or carboplatin in first-line therapy in advanced ovarian cancer (Table 1). Two studies increased the dose per cycle and one study only reduced the interval between the cycles while maintaining the same total cumulative dose (TCD) [13–15]. McGuire et al. [13] compared eight cycles of 3-weekly cisplatin 50 mg/m² and cyclophosphamide (CTX) 500 mg/m² with four cycles of 3-weekly cisplatin 100 mg/m² and CTX 1000 mg/m², which resulted in a dose-intensity factor of 2, whereas Gore et al. [14] compared six cycles of 4-weekly carboplatin at an area under the curve (AUC) of 8 mg/ml/min with four cycles of 4-weekly carboplatin AUC 12, which reached a dose-intensity factor of 1.4. Wrigley et al. [15] reduced the interval between the cycles from 4 to 3 weeks. In these three studies, no benefit was found, OS was not improved and the
Table 1. Dose intensity of first-line therapy in patients with advanced epithelial ovarian cancer reached by increased dose of cisplatin

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Standard arm</th>
<th>Experimental arm</th>
<th>DI factor</th>
<th>Increased TCD</th>
<th>Increased survival</th>
<th>Increased toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGuire et al., 1995</td>
<td>13</td>
<td>Cisplatin 50 mg/m² + CTX 500 mg/m² q 3 weekly × 8</td>
<td>Cisplatin 100 mg/m² + CTX 1000 mg/m² q 3 weekly × 4</td>
<td>2</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Gore et al., 1998</td>
<td>14</td>
<td>Carboplatin AUC 8 q 4 weekly × 6</td>
<td>Carboplatin AUC 12 q 4 weekly × 4</td>
<td>1.4</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Wrigley et al., 1996</td>
<td>15</td>
<td>Carboplatin 300 mg/m² + CTX 600 mg/m² q 4 weekly × 6</td>
<td>Carboplatin 300 mg/m² + CTX 600 mg/m² q 3 weekly × 6</td>
<td>1.3</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Joly et al., 2000</td>
<td>16</td>
<td>Cisplatin 100 mg/m² + CTX 600 mg/m² q 4 weekly × 6</td>
<td>Cisplatin 100 mg/m² + CTX 300 mg/m² + carboplatin 300 mg/m² q 4 weekly × 6</td>
<td>1.6</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Dittrich et al., 2003</td>
<td>17</td>
<td>Cisplatin 100 mg/m² + CTX 600 mg/m² q 3 weekly × 6</td>
<td>Cisplatin 100 mg/m² + carboplatin 300 mg/m² q 4 weekly × 6</td>
<td>1.6</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Conte et al., 1996</td>
<td>18</td>
<td>Cisplatin 50 mg/m² + CTX 600 mg/m² + epidoxorubicin 60 mg/m² q 4 weekly × 6</td>
<td>Cisplatin 100 mg/m² + CTX 600 mg/m² + epidoxorubicin 60 mg/m² q 4 weekly × 6</td>
<td>2</td>
<td>Yes (2×)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Jakobsen et al., 1997</td>
<td>19</td>
<td>Carboplatin AUC 4 + CTX 500 mg/m² q 4 weekly × 6</td>
<td>Carboplatin AUC 8 + CTX 500 mg/m² q 4 weekly × 6</td>
<td>1.9</td>
<td>Yes (2×)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ngan et al., 1989</td>
<td>20</td>
<td>Cisplatin 60 mg/m² + CTX 600 mg/m² q 3 weekly × 6</td>
<td>Cisplatin 120 mg/m² + CTX 600 mg/m² q 3 weekly × 6</td>
<td>2</td>
<td>Yes (2×)</td>
<td>Yes; 3-year survival 60% versus 50%</td>
<td>Yes</td>
</tr>
<tr>
<td>Kaye et al., 1996</td>
<td>22</td>
<td>Cisplatin 50 mg/m² + CTX 750 mg/m² q 3 weekly × 6</td>
<td>Cisplatin 100 mg/m² + CTX 750 mg/m² q 3 weekly × 6</td>
<td>2</td>
<td>Yes (2×)</td>
<td>Yes; 4.9-year survival 32.4% versus 26.6%</td>
<td>Yes</td>
</tr>
</tbody>
</table>

DI factor, dose-intensity factor; TCD, total cumulative dose; q, repeated; CTX, cyclophosphamide.

toxicity was significantly higher in the dose-intense arms, which resulted in significantly more treatment delays and/or dose reductions.

Joly et al. [16] and Dittrich et al. [17] increased the platinum dose intensity by adding carboplatin 300 mg/m² to cisplatin 100 mg/m² (± CTX); thus reaching a dose-intensity factor for platinum of 1.6, together with an increase in the TCD. However, no survival benefit was found, only increased toxicity.

In four studies both the dose intensity per cycle and the TCD of platinum were doubled in combination with standard dose CTX ± epidoxorubicin [18–22]. Only two of these four studies showed a benefit in OS [20–22]. However, Ngan et al. [20] included only 65 patients in a randomized study comparing the combination of CTX 600 mg/m² with cisplatin 120 mg/m² or 60 mg/m². The 3-year survival was 60% with the high-dose regimen and 30% with the low-dose regimen at the cost of increased hematologic, renal and neurotoxicity. No long-term follow-up data of this study have been published. Kaye et al. [21, 22] compared CTX 750 mg/m² combined with cisplatin 100 mg/m² and 50 mg/m². After a follow-up of 4.9 years, OS was increased from 27% to 32% with an overall relative death rate of 0.68 (P=0.043). It appeared, however, that the benefit of high-dose cisplatin was greatest during the first 2 years; the relative death rate after 2 years was 0.52 versus 1.30 after 4.9 years. Acute and late toxicity, which lasted for >4 years, were significantly higher in the high-dose group. The authors therefore recommended a lower cisplatin dose of 75 mg/m² as providing the optimal balance between efficacy and toxicity.

**Increased dose intensity by weekly cisplatin administration**

An increase in the dose intensity can also be reached by reducing the interval between cycles (Table 2). In three studies weekly cisplatin was compared with standard 3-weekly cisplatin [23–25]. With the weekly regimen a two times higher dose intensity was reached with the same TCD. Bolis et al. [23] compared nine weekly cycles of cisplatin 50 mg/m² with six cycles of 3-weekly CTX 750 mg/m² plus cisplatin 75 mg/m². Cocconi et al. [24] reported the results of six weekly versus six 3-weekly cycles of cisplatin (both at a dose of 100 mg/m²) followed by four cycles of doxorubicin and CTX in both arms. Fruscio et al. [25] compared nine weekly cycles of cisplatin 50 mg/m² with six 3-weekly cycles of cisplatin 75 mg/m². No significant differences in PFS or OS were observed between the dose-dense and control arms in the three studies, neither in the short term nor in the long term. The nonhematologic toxicity (especially ototoxicity), however, was substantial and significantly higher in the weekly arms.

**Dose-dense weekly platinum therapy in platinum-resistant patients**

In contrast to the negative outcome of dose-dense cisplatin in first-line therapy, weekly platinum combination therapy was shown to be highly effective in platinum-resistant disease (Table 3). Already in 1980, Piver et al. [26] found in 7 out of 10
patients who had become resistant to conventionally dosed platinum a response when using six weekly cycles of cisplatin at a dose of 1 mg/kg followed by 60 mg/m² every 3 weeks. Dose-dense weekly induction therapy with cisplatin 70 mg/m² in combination with daily oral etoposide or weekly paclitaxel thus reached a 1.9-fold increased dose intensity, resulted in response rates of, respectively, 46% and 65%; these values are substantially higher than the ≤10% responses with conventional platinum chemotherapy [27–29]. In these studies, the median PFS was 5 and 8 months and the median OS was 10 and 11 months, respectively. When 3-weekly paclitaxel/cisplatin was shown to be equally effective but less toxic than 3-weekly paclitaxel/cisplatin in first-line treatment [6–8], weekly paclitaxel was combined with weekly carboplatin to reduce toxicity [30]. In this latter study, six weekly cycles with paclitaxel 90 mg/m² and carboplatin AUC 4 induction therapy were followed by six cycles of 3-weekly paclitaxel 175 mg/m² and carboplatin AUC 6 [30]. The overall response rate in the platinum-resistant patients was 58%, whereas 77% of patients had disease control (response + stable disease). The median PFS was 10 months (range 1–21) and the median OS was 12 months (range 1–69). In an attempt to further increase the efficacy, the weekly regimen was continued for 18 weeks in three studies. Cadron et al. [31] used the regimen of paclitaxel 90 mg/m² and carboplatin AUC 4 on days 1 and 8 repeated (q) 21 days for six cycles; Havrilesky et al. [32] used paclitaxel 80 mg/m² and carboplatin AUC 2 on days 1, 8 and 15 q 28 days until progression, SAE or 8 cycles after CR; and Sharma et al. [33] used paclitaxel 70 mg/m² and carboplatin AUC 3 on days 1, 8 and 15 q 28 days for six cycles. In platinum-resistant patients they found response rates of 25%–38%, with the median PFS ranging from 3.2 to 8.7 months and the median OS from 6.8 to 11.4 months.

Two studies investigated dose-dense weekly paclitaxel 90 mg/m² combined with 4-weekly carboplatin AUC 5 [34, 35]. Hoekstra et al. [34] found in 5 platinum-resistant patients a response in 60%, while Lortholary et al. [35] found a response rate of 38% and a PFS of 4.9 months in 51 patients.

### dose-dense weekly paclitaxel/carboplatin in first-line therapy

The positive results with weekly paclitaxel/platinum induction therapy in platinum-resistant ovarian cancer were the basis for a randomized first-line trial in advanced disease [36]. In this trial, patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIB to IV ovarian cancer were randomized between induction therapy with six cycles weekly paclitaxel 90 mg/m² and cisplatin 75 mg/m² or carboplatin AUC 4 on days 1, 8, 15 + 29, 36, 43 followed by paclitaxel 175 mg/m² + cisplatin 75 mg/m² or carboplatin AUC 6 q 3 weekly × 3–6 cycles or carboplatin AUC 6 q 3 weekly × 6–9 cycles. Paclitaxel 90 mg/m² + cisplatin 70 mg/m² or carboplatin AUC 4 on days 1, 8, 15 + 29, 36, 43 followed by paclitaxel 175 mg/m² + cisplatin 75 mg/m² or carboplatin AUC 6 q 3 weekly × 3–6 cycles. Paclitaxel 90 mg/m² + cisplatin 70 mg/m² or carboplatin AUC 4 on days 1, 8, 15 + 29, 36, 43 followed by paclitaxel 175 mg/m² + cisplatin 75 mg/m² or carboplatin AUC 6 q 3 weekly × 3–6 cycles.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Standard arm</th>
<th>Experimental arm</th>
<th>Planned DI factor</th>
<th>Increased TCD</th>
<th>Increased survival</th>
<th>Increased toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolis et al., 1997 [23]</td>
<td>607</td>
<td>Cisplatin 75 mg/m² + CTX 750 mg/m² q 3 weekly × 6 cycles</td>
<td>Cisplatin 50 mg/m² q 1 weekly × 9 cycles</td>
<td>2</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fruscio et al., 2011 [25]</td>
<td>285</td>
<td>Cisplatin 75 mg/m² q 3 weekly × 6 cycles</td>
<td>Cisplatin 50 mg/m² q 1 weekly × 9 cycles</td>
<td>2</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cocconi et al., 1999 [24]</td>
<td>101</td>
<td>Cisplatin 100 mg/m² q 3 weekly × 6 cycles followed by CTX doxorubicin × 4 cycles</td>
<td>Cisplatin 100 mg/m² q 1 weekly × 6 cycles followed by CTX doxorubicin × 4 cycles</td>
<td>2</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Van der Burg et al., 2009 [37]</td>
<td>263</td>
<td>Paclitaxel 175 mg/m² or carboplatin AUC 6 q 3 weekly × 6–9 cycles</td>
<td>Paclitaxel 90 mg/m² + cisplatin 70 mg/m² or carboplatin AUC 4 on days 1, 8, 15 + 29, 36, 43 followed by paclitaxel 175 mg/m² + cisplatin 75 mg/m² or carboplatin AUC 6 q 3 weekly × 3–6 cycles</td>
<td>Paclitaxel 1.03, cisplatin 1.9, carboplatin 1.3</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Katsumata et al., 2009 [38]</td>
<td>631</td>
<td>Paclitaxel 180 mg/m² + carboplatin AUC 6 q 3 weekly × 26 cycles</td>
<td>Paclitaxel 80 mg/m² on days 1, 8, 15 + 29, 36 and 43 versus three cycles of standard 3-weekly paclitaxel 175 mg/m² and cisplatin 75 mg/m² or carboplatin AUC 6</td>
<td>Paclitaxel 1.3, carboplatin 1.0</td>
<td>Yes</td>
<td>Yes; PFS 10.8 months, OS 7%, P = 0.03</td>
<td>No</td>
</tr>
</tbody>
</table>

DI factor, dose-intensity factor; TCD, total cumulative dose; q, repeated.

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**Table 2.** Dose intensity of first-line therapy in patients with advanced epithelial ovarian cancer reached by weekly cycles
Table 3. Dose-dense weekly paclitaxel + carboplatin in platinum-resistant progressive ovarian cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Platinum sensitivity</th>
<th>N (evaluable)</th>
<th>RR (%)</th>
<th>CR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Toxicity Grade 3/4 % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Burg et al., 2005 [30]</td>
<td>P 90 mg/m^2 + C AUC 4 on days 1, 8, 15 + 29, 35, 42 followed by PC q 3 weekly × 6 cycles</td>
<td>All</td>
<td>62</td>
<td>64</td>
<td>10</td>
<td>11</td>
<td>20</td>
<td>23, 92, 42, 0, 20</td>
</tr>
<tr>
<td>Cadron et al., 2007 [31]</td>
<td>P 90 mg/m^2 + C AUC 4 on days 1 + 8 q 3 weekly × 6 cycles</td>
<td>All</td>
<td>33 (29)</td>
<td>66</td>
<td>21</td>
<td>9</td>
<td>18</td>
<td>24, 94, 25, 3, 9</td>
</tr>
<tr>
<td>Havrilesky et al., 2003 [32]</td>
<td>P 80 mg/m^2 + C AUC 2 on days 1, 8 + 15 q 4 weekly until PD/CR</td>
<td>All</td>
<td>29</td>
<td>83</td>
<td>55</td>
<td>11.5</td>
<td>NR</td>
<td>11, 32, 14, 0, 21</td>
</tr>
<tr>
<td>Sharma et al., 2009 [33]</td>
<td>P 70 mg/m^2 + C AUC 3 on days 1, 8 + 15 q 4 weekly × 6 cycles</td>
<td>Refractory</td>
<td>21</td>
<td>60</td>
<td>0</td>
<td>7.9</td>
<td>13.3</td>
<td>5, 30, 0, 14, 14</td>
</tr>
<tr>
<td>Hoekstra et al., 2009 [34]</td>
<td>P 80 mg/m^2 on days 1, 8 + 15 + C AUC 5 on day 1 q 4 weeks</td>
<td>All</td>
<td>20</td>
<td>85</td>
<td>75</td>
<td>–</td>
<td>NR</td>
<td>0, 35, 0, 0, 25</td>
</tr>
<tr>
<td>Lortholary et al., 2011 [35]</td>
<td>(a) P 80 mg/m^2 on days 1, 8 + 15 (b) P 80 mg/m^2 on days 1, 8 + 15 + C AUC 5 on day 1 (c) P 80 mg/m^2 + topotecan 3 mg/m^2 on days 1, 8 + 15 all regimens q 4 weekly</td>
<td>&lt;6 months</td>
<td>57</td>
<td>35</td>
<td>14</td>
<td>3.7</td>
<td>19.9</td>
<td>6, 13, 447, 32, 2</td>
</tr>
</tbody>
</table>

N, number of patients; RR, response rate; CR, complete remission; PFS, progression-free survival; PD, progressive disease; NR, not reached; OS, overall survival; q, repeated; P, paclitaxel; C, carboplatin.
dose-dense weekly group and 18 months ($P = 0.64$) in the standard 3-weekly group, and the median OS was 44 and 43 months ($P=0.86$), respectively.

The Japanese Gynecologic Oncology Group (JGOG trial no. 3016), on the contrary, showed a significant benefit in both PFS and OS in favor of the dose-dense regimen [37]. In this study, 631 eligible patients with FIGO stages II–IV disease were randomized between weekly dose-dense paclitaxel 80 mg/m² on days 1, 8 and 15 combined with 3-weekly carboplatin AUC 6, versus standard 3-weekly paclitaxel 180 mg/m² and carboplatin AUC 6. The median PFS and the 3-year OS were significantly longer in the dose-dense group: PFS was 28 months in the dose-dense group versus 17 months in the standard group (hazard ratio for progression, 0.71; 95% confidence interval, 0.58–0.88; $P=0.0015$), and the 3-year OS rate was 72% versus 65% ($P=0.03$), respectively. The response rate in the weekly dose-dense group was 56% compared with 53% in the 3-weekly standard group.

More toxicity was observed in the weekly dose-dense group; 53% of patients in the dose-dense group and also 37% of the patients in the standard 3-weekly group stopped treatment prematurely. The main reason for discontinuing treatment was hematologic toxicity. Grade 3/4 neutropenia was observed in 92% and 80% of the patients and thrombocytopenia in 44% and 38%, respectively. In the randomized study with weekly paclitaxel/platinum induction therapy, on the contrary, 15% of patients in the dose-dense regimen and 16% in the standard 3-weekly group stopped treatment prematurely [36]. Hematologic toxicity was considerably less compared with what was observed in the JGOG study; grade 3/4 neutropenia was observed in only 44% of the patients in the dose-dense group and in 32% in the standard group, whereas grade 3/4 thrombocytopenia was observed in only 12% and 5% in both groups, respectively.

discussion

The intriguing results of the JGOG dose-dense study with weekly paclitaxel 80 mg/m² on days 1, 8 and 15 combined with 3-weekly carboplatin AUC 6 are promising [37]. The median PFS for the dose-dense weekly paclitaxel/carboplatin regimen was 28 months, a significant improvement of 11 months compared with the standard 3-weekly paclitaxel 180 mg/m² and carboplatin AUC 6. The 3-year OS rate was increased from 65% in the standard group to 72% in the dose-dense weekly group. These results, however, are in sharp contrast with the phase III results of other dose-intensity studies with cisplatin, carboplatin and weekly paclitaxel/platinum induction therapy (Table 1 and Table 2). Only two of the previously performed 12 dose-intense platinum studies, both with an increased cisplatin dose per cycle and an increased cumulative platinum dose, showed a survival benefit at the cost of important long-lasting toxicity, which hampered the further development of dose-intense cisplatin [20–22]. No survival benefit was seen in the three studies with weekly cisplatin [23–25]. It is not clear why such a large difference exists between the JGOG study with weekly paclitaxel and 3-weekly carboplatin, and the study with weekly paclitaxel/platinum induction therapy. Despite the considerably higher hematologic toxicity, leading to frequent dose reductions, treatment delays and premature therapy discontinuation, and the relatively low response rate in the JGOG study, the PFS and OS are considerably longer in the dose-dense weekly paclitaxel plus 3-weekly carboplatin group of the JGOG study.

Some investigators suggested that a more prolonged administration of weekly paclitaxel/carboplatin would be more efficacious than only using weekly induction therapy followed by the 3-weekly cycles. This weekly induction regimen followed by 3-weekly paclitaxel/carboplatin cycles, however, has proved to be very effective in platinum-resistant patients with a response rate of 58% and a median PFS of 10 months, and seems to be at least as effective as continuation of weekly paclitaxel/carboplatin for six cycles in platinum-resistant patients [31, 32] (Table 3). Also, there is no evidence that the regimen with weekly paclitaxel combined with 4-weekly carboplatin is more efficacious in platinum-resistant patients [34, 35]. In the phase II study with paclitaxel 80 mg/m² on days 1, 8 and 15 and carboplatin AUC 5 on day 1 every 4 weeks for six cycles, the response rate was 38% and the PFS was only 5 months in contrast to the 10 months with weekly paclitaxel/carboplatin induction therapy. A difference between these phase II regimens and the JGOG study is a gap of 1 week in the paclitaxel administration per cycle. Although in the JGOG study no gap between the paclitaxel administrations was planned, treatment delays occurred frequently as a result of the hematologic toxicity.

Not only in the JGOG dose-dense weekly group but also in the control arm of that study (the standard 3-weekly paclitaxel/carboplatin group), severe myelosuppression was leading more to treatment delays, dose reductions and premature treatment discontinuations than observed when using standard 3-weekly paclitaxel/carboplatin therapy in the Caucasian patients. This suggests that Asian patients may be more susceptible to the toxicity of paclitaxel/carboplatin-containing treatment regimens and that their tumor cells seem to be more sensitive to paclitaxel/carboplatin. Phan et al. [38] reported a reduced drug clearance with increased toxicity and Soo et al. [39] found in a meta-analysis an increase in OS in Asian patients and a higher response rate in Asian non-small-cell lung cancer patients receiving carboplatin/paclitaxel.

Genotypes and phenotypes are thought to represent important determinants of drug efficacy in ovarian cancer [40–44]. Especially, a silent polymorphism at codon 118 in the untranslated region of ERCC1 and survival, while codon 8092A in the minimal residual disease treated with intraperitoneal paclitaxel/cisplatin, a relationship between polymorphism C8092A in the ERCC1 gene excision repair cross complementation group 1 (ERCC1) and survival [45]. Previously, the same authors showed in EOC patients with minimal residual disease treated with intraperitoneal paclitaxel/cisplatin, a relationship between polymorphism C8092A in the ERCC1 gene. Furthermore, preliminary evidence suggests that ethnic differences in the expression of allelic variants, e.g. the allele frequency of ERCC1 C and T is 70% versus 30% in Asians and 40% versus 60% in Caucasians, may result in altered pharmacokinetics and pharmacodynamics of anticancer drugs [43, 44].
conclusion

Only one (i.e. JGOG 3016) out of a total of 14 randomized dose-intensity studies in first-line therapy using weekly paclitaxel combined with 3-weekly carboplatin, and in fact the only study performed in Asian patients, showed a large difference in PFS and OS despite significant hematologic toxicity leading to dose reductions, treatment delays and premature discontinuation of treatment. Confirmatory studies with the JGOG regimen with well defined translational research are urgently needed. These studies should include Caucasian as well as Asian patients and should be stratified for tumor histotype as suggested in the recent The Cancer Genome Alas (TCGA) study [43]. Prospective pharmacogenetic analyses of the tumor i.e. single nucleotide polymorphisms in DNA repair pathways within tumor histotypes might aid in the clarification of the pharmacokinetic and pharmacodynamic impact of this schedule. It also gives more insight in the underlying molecular processes within ethnic subgroups of patients.

disclosures

The authors declare no conflict of interest.

references