The Relationship Between Chemotherapy Related Neutropenia and Survival in Ovarian Cancer

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Abstract

Objectives: Due to limited data in the literature, we aimed to determine the relationship between the development of chemotherapy-induced neutropenia and survival in patients with ovarian cancer who underwent frontline cytoreductive surgery and received adjuvant chemotherapy.

Methods: In this study, laboratory parameters in the hospital database were collected retrospectively. The rates of patients who developed neutropenia due to chemotherapy and the relationship between neutropenia and survival were analyzed using appropriate statistical methods.

Results: A total of 82 patients were included in the study. The median age was 53.3 years. Median follow-up time was 61.6 months. Median chemotherapy cycles were 6. Disease recurrence developed in 22 (26.8%) patients and 12 patients (14.6%) were died during the follow-up period. Any degree of neutropenia developed in a total of 63 (76.8%) patients during the entire chemotherapy period. There were no grade 4 neutropenia. No correlation was found between the development of neutropenia and disease free survival or overall survival.

Conclusion: There are conflicting data in the literature regarding the relationship between chemotherapy-induced neutropenia and survival in patients with ovarian cancer who are receiving adjuvant chemotherapy. In our study, no relationship was found between the development of neutropenia and survival.

Keywords: Chemotherapy, ovarian cancer, neutropenia

rect dosing. This hypothesis suggests that toxicities may determine the effective dose of the chemotherapy (CT).

The most frequently studied toxicity is neutropenia which is one of the hematological toxicities. The development of chemotherapy-induced neutropenia (C-IN) in the patient may be an indicator that an effective dose is achieved for cancer treatment. The studies assessing this hypothesis have been carried out in the last few decades and C-IN has been associated with longer survival in several cancer types. These studies were mostly performed in patients with breast and lung cancer, and a standard chemotherapy protocol was not performed in these studies. Paclitaxel plus platin-based regimen has been established as the standard adjuvant treatment following cytoreductive surgery in patients with epithelial ovarian cancer. Evaluation of C-IN and cancer outcomes seems reasonable since this standard protocol. Conflicting results have been obtained in previous studies evaluating the survival outcomes of C-IN in ovarian cancer. Aim of this study is to evaluate the relationship between C-IN and disease-free survival and overall survival in patients receiving adjuvant carboplatin + paclitaxel for ovarian cancer.

Methods

Patients who underwent frontline surgery with epithelial ovarian cancer in Tepecik Training and Research Hospital between 2010 and 2020, and then received adjuvant carboplatin + paclitaxel chemotherapy were included. Exclusion criteria were the lack of follow-up data and being younger than 18 years. The patient’s age at diagnosis, performance status, histological type of the tumor, surgical method, stage of disease, the status of recurrence, blood tests before each cycle, and whether they had granulocyte colony-stimulating factor (G-CSF) or not were recorded. Neutropenia and thrombocytopenia were evaluated before each chemotherapy cycle. Neutropenia was classified according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 if the absolute neutrophil count (ANC) lower limit of normal to 1500/mm³, grade 2 if ANC 1000 to 1500/ mm³3, grade 3 if ANC 1000 to 500/ mm³3, and grade 4 if ANC <500/mm³. C-IN was defined as any grade (grade ≥ 1), and severe neutropenia was defined as grade 3–4. Trombocytopenia was defined as a thrombocyte count <75,000/mm³. The correlation of neutropenia and thrombocytopenia with disease-free survival (DFS) and overall survival (OS) was examined. DFS was defined as the time from surgery to recurrence date of disease, and OS as the time from surgery to the date of death or the date of last visit. According to the time of developing the first neutropenia, patients were divided into 2 groups (first 3 cycles and last 3 cycles). In the evaluation of the data, descriptive statistics, means, median values and standard deviations of the patients were calculated. Statistical analysis was performed with chi square, Fisher’s exact test, and Student’s t-test where appropriate using Statistical Program for Social Science (SPSS) version 24.0. Survival curves were calculated with Kaplan–Meier method with log rank for significance. Median follow-up time was calculated by reverse Kaplan-Meier analysis. The statistical significance level was accepted as p<0.05.

Results

The study included 82 patients with stage 1-4 epithelial ovarian cancer who received adjuvant carboplatin + paclitaxel after primary surgery. The median age was 53.3 years (range: 23-77) at the time of diagnosis. Sixty-eight percent three percent of patients were postmenopausal. Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 84.1 %, and 1 in 15.9 %. Histological features and tumor stage distribution were shown in Table 1. Only 1 of 82 patients received a weekly paclitaxel + carboplatin as adjuvant CT, and the others received the standard 3 weekly regimen. The number of median CT cycles applied was 6 (2-8). Sixty three point four percent of the patients were able to receive planned treatments without postponement. Four point nine percent of the patients who were evaluated to the surgery were initially decided as inoperable. All remaining patients underwent frontline cytoreductive surgery (95,1%). Optimal cytoreduction was performed in 89% of patients. While optimal cytoreduction could not be achieved in 9 patients (11%).

The median follow-up period was 61,6 months. During the follow-up, disease recurrence developed in 22 (26.8%) of

<table>
<thead>
<tr>
<th>Histology</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometroid</td>
<td>12</td>
<td>14.6</td>
</tr>
<tr>
<td>Serous</td>
<td>50</td>
<td>61.0</td>
</tr>
<tr>
<td>Clear cell</td>
<td>6</td>
<td>7.3</td>
</tr>
<tr>
<td>Musinous</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Mixt</td>
<td>5</td>
<td>6.0</td>
</tr>
<tr>
<td>Low grade serous</td>
<td>3</td>
<td>3.7</td>
</tr>
<tr>
<td>Transisoneel cell carcinoma</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Bordeline serous</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>25</td>
<td>30.5</td>
</tr>
<tr>
<td>Stage 2</td>
<td>6</td>
<td>7.3</td>
</tr>
<tr>
<td>Stage 3</td>
<td>49</td>
<td>59.8</td>
</tr>
<tr>
<td>Stage 4</td>
<td>2</td>
<td>2.4</td>
</tr>
</tbody>
</table>
the patients. Fifteen of these 22 patients had peritoneal implant, 5 of them had distant metastasis, and 2 of them had lymph node metastasis. At the time of data cut-off, 12 patients (14.6%) were died. Before the first cycle non of the patients had thrombocytopenia, and 13 of them (15.8%) had grade 1 neutropenia (ANC 1500-2500/mm). The mean thrombocyte count was 324.109±112.981, and the mean neutrophil was 4341.9±1509.7. There was no neutropenia in 20 (24.3%) patients during the treatment period. Grade 1 neutropenia developed in 43 (52.4%) patients, grade 2 neutropenia developed in 15 (18.3%) patients, grade 3 neutropenia in 5 (6%) patients. Grade 4 neutropenia were not developed in any patients. Seventeen of the patients (20.7%) had used G-CSF in any cycles of chemotherapy. The rates of patients with C-IN per cycle and their relationship with DFS and OS were shown in Table 2. The development of C-IN in any cycle was not associated with DFS and OS. The number of patients developing thrombocytopenia was 10 (12.2%) in all cycles. Chemotherapy-induced thrombocytopenia was not associated with OS and DFS.

Only 5 patients (6%) developed severe (grade ≥3) neutropenia. There was no recurrence or death in any of these 5 patients. The other's (grade 0-2) 5-year DFS was 68 % and OS was 79% respectively. There was no statistically significant difference between the 2 groups for DFS (p=0.190) and OS (p=0.373). 5-year DFS rate of the patients developing first C-IN in first 3 cycle was 65% and, in last 3 cycle was 74% (p=0.636). 5- year OS rate in first group was 68% and, in last group was 87% (p=0.075) (Fig. 1). C-IN was developed in 34 patients in the first 3 cycles. CT was delayed in 52.9% of them. There were 25 patients who developed C-IN in the last 3 cycles. CT was delayed in 20% of them (p=0.010).

### Discussion

The majority of patients with ovarian cancer experience a disease recurrence. Tumor stage, residual disease after initial surgery, histological type, and tumor grade are the most important clinical-pathological predictors for survival outcomes. In addition to these prognostic markers in patients diagnosed with ovarian cancer, studies on many prognostic and predictive biomarkers are ongoing.[11,14] Chemotherapy-induced myelotoxicity has been proposed as a potential prognostic factor for ovarian cancer. We did not find a significant correlation between chemotherapy-induced neutropenia and DFS and OS in patients with epithelial ovarian cancer who received adjuvant carboplatin.

### Table 2. DFS and OS of the patients with and without C-IN according to cycles

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Grups</th>
<th>DFS rate (%)</th>
<th>p</th>
<th>Survival rate (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3 year/5 year</td>
<td></td>
<td>3 year/5 year</td>
<td></td>
</tr>
<tr>
<td>Before 2</td>
<td>C-IN (+) n=13</td>
<td>76/76</td>
<td>0,819</td>
<td>80/80</td>
<td>0,850</td>
</tr>
<tr>
<td></td>
<td>C-IN (-) n=69</td>
<td>74/69</td>
<td></td>
<td>90/80</td>
<td></td>
</tr>
<tr>
<td>Before 3</td>
<td>C-IN (+) n=31</td>
<td>72/67</td>
<td>0,741</td>
<td>82/72</td>
<td>0,121</td>
</tr>
<tr>
<td></td>
<td>C-IN (-) n=51</td>
<td>75/72</td>
<td></td>
<td>93/85</td>
<td></td>
</tr>
<tr>
<td>Before 4</td>
<td>C-IN (+) n=33</td>
<td>71/66</td>
<td>0,571</td>
<td>80/74</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-IN (-) n=49</td>
<td>76/73</td>
<td></td>
<td>94/84</td>
<td>0,169</td>
</tr>
<tr>
<td>Before 5</td>
<td>C-IN (+) n=46</td>
<td>70/66</td>
<td>0,450</td>
<td>87/76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-IN (-) n=36</td>
<td>80/75</td>
<td></td>
<td>90/85</td>
<td>0,448</td>
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<tr>
<td>Before 6</td>
<td>C-IN (+) n=40</td>
<td>71/67</td>
<td>0,537</td>
<td>88/80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-IN (-) n=42</td>
<td>77/73</td>
<td></td>
<td>92/80</td>
<td>0,923</td>
</tr>
<tr>
<td>Any cycle</td>
<td>C-IN (+) n=62</td>
<td>71/68</td>
<td>0,352</td>
<td>85/76</td>
<td></td>
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<tr>
<td></td>
<td>C-IN (-) n=20</td>
<td>84/77</td>
<td></td>
<td>100/90</td>
<td>0,140</td>
</tr>
<tr>
<td>Any cycle</td>
<td>Thrombocytopenia (+) n=10</td>
<td>58/58</td>
<td>0,284</td>
<td>90/60</td>
<td>0,449</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia (-) n=57</td>
<td>72/70</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Figure 1. Overall survival patients with first neutropenia on first cycle and after 3 cycle.](image-url)
shown in breast and lung cancer, while there were less data on ovarian cancer. The probable reason for this is the use of carboplatin in ovarian cancer and the dose adjustment of it with the area under the curve (AUC). AUC dosing may prevent underdosing more than dosing strategies based on body surface area (BSA). In our study, patients were divided into two groups and evaluated according to the time of first neutropenia development. Patients whose first neutropenia developed in the last 3 cycles showed a better overall survival (87% vs 68%, \( p=0.075 \)), although it did not reach statistical significance compared to those who developed in the first 3 cycles. When we evaluated the CT delay rates in these groups, we found that the CT delay rate was statistically significantly lower in the group with better survival (20% vs 52.9% \( p=0.010 \)). Therefore, we thought that although the difference in survival between the two groups did not reach significance, it might be due to dose intensity in the better group. The most important limitations were the retrospective nature of our study and the small number of patients. The use of G-CSF was an exclusion criterion in all similar studies in the literature. In our study, 20% of the patients received G-CSF. Actually, C-IN was partially masked in our study. The strength of the study was that correlation between neutropenia and prognosis was evaluated in both any grade and severe neutropenia. In addition, DFS and OS were analyzed separately for each cycle.

**Conclusion**

Conflicting results have been obtained in studies examining the relationship between the development of chemotherapy-related neutropenia and survival in ovarian cancer patients receiving adjuvant chemotherapy. We could not find a relationship between C-IN and ovarian cancer survival in our study. Our study was one of the negative studies.

**Disclosures**

**Ethics Committee Approval:** Tepecik Education and Research Hospital Ethics Committee approved the study (Date: 12.08.2020 No: 2020/10-2).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.


**References**

2. Eskander RN, Tewari KS. Impact of chemotherapy-induced


