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Research Article

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 survial.

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

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Today, Almost all clinicians use body surface area (BSA) for the dosing of conventional cytotoxic chemotherapy agents in daily oncology practice. It's hard to say that this is an ideal method because it's calculated using just body height and weight. However, the pharmacokinetics and pharmacodynamics of the chemotherapeutic agent in each person may vary according to individual differences and genetic backgrounds, and the dose given to each patient may not reach the effective dose or may reach toxic doses. Furthermore, there is not enough data to support this BSA-based strategy. Gurney introduced the limitations of BSA-based dose calculation nearly 20 years ago, a method that does not take into account the highly complex process of elimination of cytotoxic drugs.[1] Because of this BSA-based method of dose calculation, it is possible that up to 30% of patients will inadvertently remain at low plasma levels of chemotherapeutics. Therefore, some researchers argue that drug-specific toxicity may be a good indicator for cor-

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rect dosing.[2] 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.[3-7] 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.[8,9] 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.[10-14] 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.[15] Grade 1 if the absolute neutrophil count (ANC) lower limit of normal to 1500/mm^3, grade 2 if ANC 1000 to 1500/ mm31500/mm^3, grade 3 if ANC 1000 to 500/ mm3, and grade 4 if ANC <500/mm^3. 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/mm^3. 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 point 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 1. Histologic features and stages of the tumors

	n	%
Histology		
Endometroid	12	14.6
Serous	50	61.0
Clear cell	6	7.3
Musinous	2	2.4
Mixt	5	6.0
Low grade serous	3	3.7
Transisonel cell carsinoma	1	1.2
Carcinosarcoma	2	2.4
Bordeline serous	1	1.2
Stage		
Stage 1	25	30.5
Stage 2	6	7.3
Stage 3	49	59.8
Stage 4	2	2.4

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).

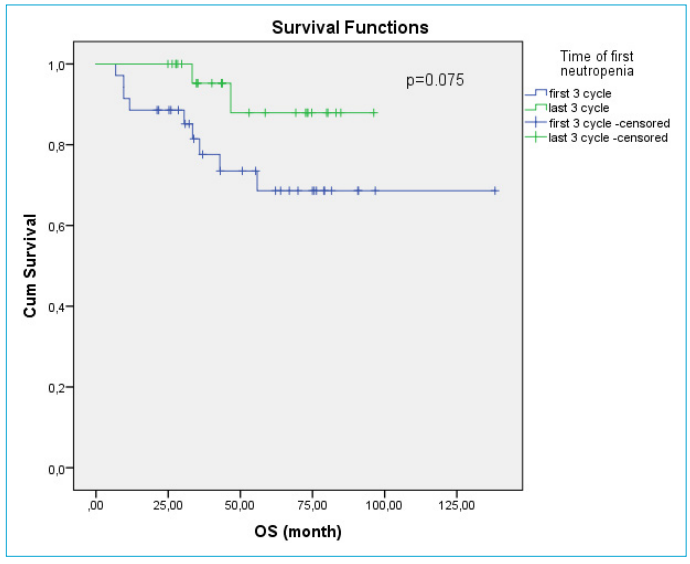

Figure 1. Overall survival patients with first neutropenia on first cycle and after 3 cycle.

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

Cycle	Grups	DFS rate (%) 3 year/5 year	p	Survival rate (%) 3 year/5 year	p
Before 2	C-IN (+) n=13	76/76	0,819	80/80	0,850
	C-IN (-) n=69	74/69		90/80	
Before 3	C-IN (+) n=31	72/67	0,741	82/72	0,121
	C-IN (-) n=51	75/72		93/85	
Before 4	C-IN (+) n=33	71/66	0,571	80/74	
	C-IN (-) n=49	76/73	94/84	0,169	
Before 5	C-IN (+) n=46	70/66	0,450	87/76	
	C-IN (-) n=36	80/75	90/85	0,448	
Before 6	C-IN (+) n=40	71/67	0,537	88/80	
	C-IN (-) n=42	77/73	92/80	0,923	
Any cycle	C-IN (+) n=62	71/68	0,352	85/76	
	C-IN (-) n=20	84/77	100/90	0,140	
Any cycle	Thrombocytopenia (+) n=10	58/58	0,284	90/60	0,449
	Thrombocytopenia (-) n=57	72/70		86/78	

plus paclitaxel in this study. There were studies in the literature showing different results. In a study conducted by Kim et al (n=130), PFS and OS were improved in patients with ovarian cancer who developed C-IN but did not reach statistical significance.[11] In this study, patients using G-CSF were excluded and the cutoff value for neutropenia was 1000/mm^3 in opposite to our cut-off value for neutropenia. Grade 3-4 neutropenia developed in 75% of the patients in this study. The fact that the rate of development severe neutropenia was much higher compared to our study despite using the same treatment regimen may be due to the exclusion of patients using G-CSF. In our study, the rate of use of G-CSF was 20.7%. Rocconi et al reported improvement in PFS and OS in patients with ovarian cancer who developed neutropenia with platinum and taxane-based chemotherapy.[13] PFS was 14 vs. 6 months (p=0.01), OS was 45 vs. 29 months (p=0.03) in this study, and neutropenia was defined as ANC <1000/mm^3. Our study defined neutropenia as ANC <2500/mm^3, and severe neutropenia as ANC <1000/mm^3. Only 5 patients (6%) developed severe neutropenia, and none of these 5 patients had disease recurrence or death. In addition, the use of G-CSF was an exclusion criterion in Rocconi's study, and 80% of the patients developed neutropenia. There was no such limitation in our study; probably for this reason, the number of patients who developed severe neutropenia was small. The most comprehensive study on this subject was conducted by the Gynecological Oncology Group with 3447 patients.[14] Tewari et al. showed in this study that, neutropenic patients experienced significantly improved survival compared to non-neutropenic patients with the adjusted hazard ratio (HR) for death being 0.86 (95% confidence interval 0.74–0.99; p=0.041). Different treatment regimens were used in this study, the use of GCSF was not allowed and the neutropenia limit was determined as 1000/mm^3. The small number of our patients, not exclusion of patients using G-CSF, and different cut-off values for the definition of neutropenia may be possible reasons why our study did not obtain similar results. Contrary to these two studies, in a study conducted by Daniele et al, no correlation was found between the development of any grade neutropenia or severe neutropenia and survival in patients with ovarian cancer.[16] The use of G-CSF was not allowed in this study either. In patients who developed severe neutropenia (ANC<500/mm^3), a 20% dose reduction was performed. In addition, Daniele et al performed a meta-analysis that included data from two other studies.[11,14] Any degree of neutropenia was not associated with PFS and OS in this meta-analysis. The authors' interpretation was that the association between C-IN and cancer prognosis was mostly 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).

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Conflict of Interest: None declared.

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References

1. Gurney H. Dose calculation of anticancer drugs: a review of the current practice and introduction of an alternative. J Clin Oncol. 1996; 14: 2590-2611
2. Eskander RN, Tewari KS. Impact of chemotherapy-induced

neutropenia on survival in patients with breast, ovarian and cervical cancer: a systematic review. Journal of Hematological Malignancies. 2012;2(3):63-73.

3. D.A. Cameron, C. Massie, G. Kerr, R.C. Leonard, Moderate neutropenia with adjuvant CMF confers improved survival in early breast cancer, Br. J. Cancer 89 (2003) 1837–1842.
4. M. Di Maio, C. Gridelli, C. Gallo, F. Shepherd, F.V. Piantedosi, S. Cigolari, et al., Chemotherapy-induced neutropenia and treatment efficacy in advanced nonsmall-cell lung cancer: a pooled analysis of three randomised trials, Lancet Oncol. 6 (2005) 669–677.
5. S. Khan, A. Dhadda, D. Fyfe, S. Sundar, Impact of neutropenia on delivering planned chemotherapy for solid tumours, Eur. J. Cancer Care 17 (2008) 19–25.
6. K. Shitara, K. Matsuo, I. Oze, A. Mizota, C. Kondo, M. Nomura, et al., Meta-analysis of neutropenia or leukopenia as a prognostic factor in patients with malignant disease undergoing chemotherapy, Cancer Chemother. Pharmacol. 68 (2011) 301–307.
7. K. Shitara, K. Matsuo, D. Takahari, T. Yokota, Y. Inaba, H. Yamaura, et al., Neutropaenia as a prognostic factor in metastatic colorectal cancer patients undergoing chemotherapy with first-line FOLFOX, Eur. J. Cancer 45 (2009) 1757–1763.
8. McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med. 1996;334:1–6.
9. Piccart MJ, Bertelsen K, James K, Cassidy J, Mangioni C, Simonsen E, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst. 2000;92:699–708.
10. Carus, H. Gurney, V. Gebski, P. Harnett, R. Hui, R. Kefford, et al., Impact of baseline and nadir neutrophil index in non-small cell lung cancer and ovarian cancer patients: assessment of chemotherapy for resolution of unfavourable neutrophilia, J. Transl. Med. 11 (2013) 189.
11. J.J. Kim, J.Y. Park, D.Y. Kim, J.H. Kim, Y.M. Kim, J.H. Nam, et al., Is chemotherapy induced neutropenia a prognostic factor in patients with ovarian cancer? Acta Obstet. Gynecol. Scand. 89 (2010) 623–628.
12. C.K. Lee, H. Gurney, C. Brown, R. Sorio, N. Donadello, G. Tulunay, et al., Carboplatin paclitaxel-induced leukopenia and neuropathy predict progression-free survival in recurrent ovarian cancer, Br. J. Cancer 105 (2011) 360–365.
13. R.P. Rocconi, K.S. Matthews, M.K. Kemper, K.E. Hoskins, M.N. Barnes, Chemotherapy related myelosuppression as a marker of survival in epithelial ovarian cancer patients, Gynecol. Oncol. 108 (2008) 336–341.
14. K.S. Tewari, J.J. Java, T.A. Gatcliffe, M.A. Bookman, B.J. Monk, Chemotherapy-induced neutropenia as a biomarker of survival in advanced ovarian carcinoma: an exploratory study of the gynecologic oncology group, Gynecol. Oncol. 133 (2014) 439–445.
15. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 2017, National Institutes of Health, National Cancer Institute. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf (Accessed March 4, 2023).
16. Daniele G, Arenare L, Scambia G, Pisano C, Sorio R, Breda E et al. Prognostic role of chemotherapy-induced neutropenia in first-line treatment of advanced ovarian cancer. A pooled analysis of MITO2 and MITO7 trials. Gynecol Oncol. 2019 Jul;154(1):83-88.