

Toxicity management and efficacy of carboplatin desensitization therapy for recurrent epithelial ovarian carcinoma

A real-world study

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Abstract

Epithelial Ovarian cancer (EOC) is the most lethal gynecologic cancer worldwide. Carboplatin (CP) is the main chemotherapeutic agent in the treatment of ovarian cancer. However, the development of a hypersensitivity reaction (HSR) in 10% to 15% of patients with EOC is an important limiting factor for the clinical use of CP. Herein, we aimed to investigate the efficacy and safety of CP-desensitization (CP-D) therapy in the treatment of recurrent patients with EOC. Forty-seven ovarian cancer cases treated with CP-desensitization at the Istanbul University Oncology Institute were retrospectively analyzed between 01.01.2017 and 01.01.2022. The decision for CP-D was based on the patients' history of HSR and/or a positive skin test. For all patients, a 6-hour 12-step rapid drug desensitization protocol with a 30-minutes premedication regimen was used. Forty-seven patients were included in this study, and the median age at diagnosis was 53 years (range; 27–80). Twenty-one (43.7%) patients had 1 or more comorbid diseases, and 12.7% had a previous history of drug allergy. On average, HSR due to carboplatin was identified after 9 (7–16) cycles, and carboplatin was administered $n = 11$ (range, 3–36) times to patients. The overall survival from the first desensitization procedure (OS2) was 42.2 months (range: 25.3–59.1), and the 1-, 2-, and 5-years survival rates were 92.6%, 75.6%, and 47.2%, respectively. The objective response rate (ORR) was 78.5%. Cumulatively, 496 CP-D procedures were performed, of which 478 (96.3%) were successfully completed. None of the patients included in this study developed severe (grade 3–4) HSR during CP administration (no adrenaline was used, no need for intensive care). No deaths due to CP-D were noted. CP-D is a beneficial and safe method in treating platinum-sensitive recurrent EOC patients with CP-induced HSR.

Abbreviations: CP = carboplatin, CP-D = carboplatin desensitization, CR = complete response, EOC = epithelial ovarian cancer, HSR = hypersensitivity reaction, ORR = objective response rate, OS = overall survival, PFS = progression free survival, PR = partial response.

Keywords: carboplatin, chemotherapy, desensitization, hypersensitivity, ovarian carcinoma

1. Introduction

Ovarian cancer is the second most common gynecological cancer among women worldwide.^[1] More than 90% of ovarian cancers originate from the epithelium, of which 70% to 80% are high-grade serous carcinomas, and other common types include low-grade serous, mucinous, endometrioid, and clear cell adenocarcinomas. Epithelial ovarian cancer (EOC) is the most lethal gynecological cancer.^[2] Today, platinum-based chemotherapy, following optimal debulking surgery, remains the backbone of EOC treatment.^[2,3] Despite all aggressive frontline treatments, most EOCs have a high recurrence rate of 70% to 80%, and the 5-year survival is less than 50%.^[2–4] EOC is traditionally divided into 2 groups according to the time of

recurrence: platinum-resistant EOC when the last platinum use was less than 6 months, and platinum-sensitive EOC when the last platinum use was more than 6 months.^[2] Platinum sensitivity is 1 of the most important prognostic factors that determine the course of the disease.^[2,5]

Carboplatin (CP) is the main chemotherapeutic agent in the treatment of ovarian cancer.^[6,7] However, the development of a hypersensitivity reaction (HSR) noted in approximately 10% to 15% of patients with ovarian cancer is an important limiting factor for the clinical use of CP.^[8–11] Furthermore, previous studies have reported HSR have been in up to 27% of patients treating more than 7 cycles use of CP has been reported.^[8,9] CP-related HSR may occur within minutes or even hours after infusion, and it is characterized by the

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development of mild symptoms, such as erythema, pruritus, and urticaria, as well as severe symptoms, including difficulties in breathing, hypotension, anaphylaxis, cardiovascular collapse, and even death.^[9] Previous history of drug allergies, cumulatively receipt of > 7 CP cycles, and sensitivity to other platinum derivatives (cross-reaction) are among the most prominent risk factors for HSR.^[10,12] Moreover, recent studies have shown that HSR is linked to an increased risk in BRCA mutations.^[13,14] CP-induced HSR occurs most commonly at 7 to 8 CP cycles (usually at first relapse), and often results in treatment discontinuation.^[9,10,12]

Drug desensitization depends on the drug that causes the HSR, and introduces a temporary state of tolerance to a drug that causes. Usually, this process is initiated at low doses, followed by gradually increasing doses in longer than the normal infusion time, and it may also involve premedication with steroid and antihistamine drugs.^[10,15] CP is vital in the treatment of platinum-sensitive recurrent EOC. However, the risk of cross-reaction with other platinum derivatives, which are significantly more toxic compared to CP, and the lower efficacy of alternative non-platinum chemotherapy agents underline the importance of carboplatin desensitization (CP-D) in treating platinum-sensitive recurrent EOC patients with CP-induced HSR.^[10,14-16]

Previous studies have shown that CP-D is a safe and effective method in the treatment of ovarian cancer treatment, even when performed under different protocols.^[10,11,14-19] The 12-step 6-hour rapid desensitization protocol developed by Lee et al in 2004 is one of the most effective and safe protocols used in clinical practice,^[15] which is also used in our clinic. This regimen was used in all patients included in the study. To our knowledge, the studies on the effectiveness of CP-desensitization therapy in patients with recurrent ovarian cancer are limited in literature. Therefore, this study aimed to investigate the efficacy and safety of CP-desensitization therapy in the treatment of recurrent ovarian cancer.

2. Methods

Forty-seven ovarian cancer cases treated with CP-desensitization were retrospectively analyzed between 01.01.2017 and 01.01.2022.

Patients (≥ 18 years old) with platinum-sensitive recurrent EOC, who had experienced CP-induced HSR, were included in this study. All patients had previously received CP therapy in adjuvant and/or neo-adjuvant settings.

Baseline clinical and demographic data were collected, including age, comorbidities, such as diabetes, hypertension, chronic kidney disease, and ischemic heart disease, history of drug allergy, body mass index, tumor histology, previous number of chemotherapy regimens, degree of cytoreduction, and overall survival.

HSR was considered mild in cases of localized cutaneous reactions alone, including localized urticaria or pruritus. In contrast, HSR was considered moderate to severe in cases presenting with diffuse skin reaction, wheezing-dyspnea, bronchospasm, oxygen desaturation, hypotension, and cardiac collapse. The clinical decision for CP-desensitization was based on clinical findings and/or skin tests. All patients were discussed in the institutional local tumor board for gynecological cancer in terms of re-administration of carboplatin treatment with desensitization, switching to alternative regimens, or only provide optimal supportive care.

Our center is well-equipped and experienced cancer institute in Turkey, and there is a special ward in the chemotherapy unit with trained nurses and clinical personnel that is specially equipped for desensitization, with rapid intervention opportunities. In addition, an experienced responsible physician has been working in this treatment unit during the entire desensitization process.

In this study, we used the 12-step 6-hour rapid drug desensitization protocol presented by Lee et al in 2004.^[15]

First, all life-threatening risks, including death during desensitization, and potential benefits of this treatment were explained in detail, and informed consent was obtained from all patients before the desensitization procedure.

Second, premedication therapy was administered 30 minutes before the start of desensitization therapy. All patients were intravenously treated with glucocorticoids (dexamethasone or methylprednisolone), H1 and H2 antagonists (famotidine and chlorpheniramine), and lorazepam for anxiety if necessary.

The standard 12-step desensitization protocol combined gradual increases in the infusion rate and concentration of CD, administering the total CD dose over 5.82 hours (Table 1).

When HSR developed during desensitization, it was evaluated by the responsible physician. When grade 3 or higher HSR was diagnosed, the carboplatin infusion was stopped immediately and adrenaline was recommended. When the diagnosis of mild HSR was made, treatment was interrupted, antihistamine and steroid were administered, 1 hour was given for the symptoms to regress, and carboplatin infusion

Table 1

The 12-step 6-h rapid drug desensitization protocol defined by Lee et al in 2004.

Standard desensitization protocol using a total dose of 500 mg as an example					
Total dose	500 mg	Solution concentration	Total dose in each solution (mg)		
Solution A	250 mL	0.02 ng/mL	5.0*		
Solution B	250 mL	0.20 ng/mL	50.0*		
Solution C	250 mL	2.00 ng/mL	500.0*		
Step	Solution	Rate (mL/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	A	2	15	0.010	0.010
2	A	5	15	0.025	0.035
3	A	10	15	0.050	0.085
4	A	20	15	0.100	0.185
5	B	5	15	0.250	0.435
6	B	10	15	0.500	0.935
7	B	20	15	1.000	1.935
8	B	40	15	2.000	3.935
9	C	10	15	5.000	8.935
10	C	20	15	10.000	18.935
11	C	40	15	20.000	38.935
12	C	75	15	461.065	500.000

Total time = 5.82 h

Total dose infused = 500 mg*

was allowed to be restarted after the symptoms resolved during this period. If mild HSR recurred on desensitization, the same procedure was repeated. However, if symptoms still did not improve within 1 hour, discontinuation of treatment was recommended.

2.1. Survival outcomes

In accordance with the Response Evaluation Criteria in Solid Tumors (1.1) published rules, the best responses to treatment were classified into the following 4 subgroups: complete response (CR), partial response (PR), stable disease (SD), and progressive disease. The primary endpoint was the success rate of CP-D administration in all patients. The secondary endpoints involved the progression free survival (PFS), overall survival (OS), and objective response rate (ORR) of CP therapy. OS was defined as the time from the onset of salvage therapy until disease-related death. Patients’ death dates were obtained from the death notification system of the Ministry of Health. PFS was considered as the time from the onset of salvage therapy to the first record of radiological tumor progression, and ORR was Defined as the proportion of patients with partial or complete response to therapy. Response Evaluation Criteria in Solid Tumors 1.1 was used to evaluate the extent of tumor progression. Adverse events were analyzed using the National Cancer Institute’s Common Terminology Criteria for Adverse Events version 5.0). For the grade of adverse events, Show to Table 2.

2.2. Statistical analysis

IBM SPSS Statistics for Windows (Version 25.0; Armonk, NY: IBM Corp.) was used for all statistical analyses. For descriptive statistics, categorical variables were expressed as numbers and percentages. Proportions in independent groups were analyzed by the Chi-square test. Comparisons of the numerical variables in 2 independent groups were performed using Student’s *t* test, as the condition for normal distribution was met. Survival rates were calculated using the Kaplan–Meier method. Univariate analysis of PFS and OS was performed using the log-rank test. Risk factors were analyzed by Cox regression analysis. The statistical significance level of alpha was set to *P* < .05.

3. Results

Forty-seven patients were included in this study with a median age at diagnosis of 53 years (range: 27–80). Table 3 summarizes

treatment details for the patients in this study. The median body mass index was 29.6 (range: 20–41.6). Twenty-one (43.7%) patients had 1 or more comorbid diseases and 12.7% had a previous history of drug allergy. While 89.4% of cases were high-grade serous carcinoma, 11.6% had non-serous histology. At the time of diagnosis, 91.4% of patients had advanced stage (stage 3–4) disease. Twelve patients (25.5%) received neo-adjuvant chemotherapy.

HSR due to carboplatin was identified on average after 9 (7–16) cycles. Carboplatin was administered an average of 11 (3–36) times with desensitization. The OS from diagnosis (OS1) was 121.3 months (range: 72.2–170.4), while the OS from the first desensitization procedure (OS2) was 42.2 months (range: 25.3–59.1). The OS curves were presented in Figure 1. The 1-, 2-, and 5-year survival rates were 92.6%, 75.6%, and 47.2%, respectively. The best response rates were as follows: CR, 12 (25.4%); PR, 25 (53.1%); SD, 7 (14.8%); progressive disease, 3 (6.3%). ORR and DRR were 78.5% and 93.7%, respectively. Responses to the treatment and survival were presented in Table 4. Furthermore, 19.1% of patients had BRCA mutation, and univariate analysis revealed no significant differences between the survival for OS1 (*P* = .584) and OS2 in BRCA mutant patients (*P* = .537).

Cumulatively, 496 desensitization procedures were performed on all patients, of which 478 were successfully completed (96.3%). During the initial HSR, prior to desensitization, patients most commonly presents with pruritus at 61.7% (29 of 47) (Table 5). A comparison of the symptoms before and after desensitization showed that mild symptoms were similar, while there was a decrease in the frequency of moderate and severe side effects in patients who underwent desensitization. Moderate to severe HSR was only observed in 10.6% of patients (5/47) during CP-D. In such cases, rapid intervention was performed, and infusion was interrupted. Fluid replacement, oxygen support, and steroid and antihistamine treatments were applied, and all complaints were well-controlled without using adrenaline. No need for intensive care and no deaths due to desensitization were observed.

4. Discussion

CP is especially vital in the treatment of platinum-sensitive recurrent EOC.^[5] In this study, we investigated the efficacy and safety of CP-desensitization therapy in patients with platinum-sensitive recurrent EOC. A total of 496 cycles of desensitization were performed in 47 patients, and 96.3% were successfully completed. Furthermore, there were no cases requiring intensive care or adrenaline use, and no deaths. ORR was 78.5% and the 2- and 5-year OS2 were 75.6% and 47.2%, respectively.

CP is the main chemotherapeutic agent in the treatment of ovarian cancer.^[6,7] However, HSRs, the risk of which increases with repeated CP use, limit the utility of this chemotherapy treatment. As a result, carboplatin therapy is often discontinued when a HSR occurs. The risk of cross-reaction with other platinum derivatives, which are significantly more toxic compared to CP, and the lower efficacy of alternative non-platinum chemotherapy agents underline the importance of carboplatin desensitization (CP-D) in treating platinum-sensitive recurrent EOC patients with CP-induced HSR.^[10,14–16]

Carboplatin-induced HSR is often IgE-mediated.^[10,12] Therefore, an effective premedication could reduce the development of HSR, but not completely prevent it from occurring.^[10] Carboplatin desensitization has been used in the treatment of gynecological cancer for many years, and many different desensitization protocols have been developed. Previous studies have shown that desensitization is effective and safe^[10,11,14–19]; however, studies evaluating the efficacy and safety of carboplatin in the treatment of recurrent ovarian cancer are limited.

Table 2
Grading system for allergic reactions and anaphylaxis based on the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0.

	Allergic reaction	Anaphylaxis
Grade	Clinical symptoms	
0	No reaction	No reaction
1	Systemic intervention not indicated	-
2	Oral intervention indicated	-
3	Bronchospasm, hospitalization indicated for clinical sequelae; intravenous intervention indicated	Symptomatic bronchospasm, with or without urticaria, parenteral intervention indicated; allergy-related edema/angioedema, hypotension
4	Life-threatening consequences: urgent intervention indicated	Life-threatening consequences: urgent intervention indicated
5	Death	Death

Table 3
Demographic and clinical features of patients.

	N (47)	%	
Age*	53 ± 13	27–80	
Body mass index*	29.6 ± 5.5	20.0–41.6	
BRCA mutation	9	19.1	
Comorbidities	21	43.7	
History of drug allergy	6	12.7	
Histology	Serous (high-grade)	42	89.4
	Non-serous	5	10.6
Desensitization decide	History of prior HSR	24	51
	Positive CP skin test	23	49
Stage at diagnosis	1–2	4	8.6
	3–4	43	91.4
Neo-adjuvant chemotherapy	Yes	12	25.5
	No	35	75
Number of CP cycle develop	9.6 ± 2.3	7–14	
HSR: median (range)			
Cycles of desensitization treatment	11.0 ± 8.5	3–36	
Success desensitization rate	478 of total 496 cycles,	96.3%	

CP = carboplatin, HSR = hypersensitivity reaction.

In a study conducted by Alterwerger et al in 2016, 129 patients underwent 3.5 hours rapid CD and successfully completed 96% of 788 cycles.^[16] Another study by Alterwerger et al in 2018 evaluated the impact of CD treatment on recurrent EOC,^[14] comparing patients with CD-HSR and desensitization with those without CD-HSR. Patients treated with carboplatin desensitization (131 months vs 83 months, $P = .009$) had longer survival rates.

This finding can be explained by tumor regression secondary to CP-related T cell activation, IgE, and increase in

cytokines in patients who develop HSR. In the sub-group of BRCA mutant patients with CP allergy and desensitization, OS did not demonstrate significant differences. Our findings on BRCA mutant patients are consistent with the results of this study.

In a prospective study conducted by Nishimura *et al* in 2021, a 4-step 2-hour rapid desensitization protocol was applied to 22 patients with 90.9% success, and ORR and OS were 63.6 months and 23.8 months, respectively.^[18] An interesting aspect of that study was that no treatment-related deaths were observed in patients who developed a grade 3 reaction and were not treated with adrenaline. Similarly, our study showed that severe (grade 3) side effects, although observed less frequently, were controlled with fluid replacement and steroid and antihistamine treatment, without using adrenaline.

In a study conducted by Park et al in 2020, 104 desensitization cycles were performed on 21 patients, with a success rate of 96.3%.^[17] Interestingly, no differences were observed in drug efficacy and frequency of severe (grade 3–4) side effects (except HSR), such as bone marrow suppression, between patients with and without carboplatin desensitization.

In a retrospective study conducted by Yamamoto et al in 2022, a 4-step 2-hour rapid desensitization protocol was applied in 15 patients. Results showed that 93.4% of a total of 91 cycles were successfully completed, and the ORR was 82.6%.^[19]

In our study, ORR and DCR were 78.5% and 93.7%, respectively. Our findings are consistent with the results of previous studies.^[14–19] In our study, OS2 (from the desensitization procedure) was 42.2 months (range: 25.3–59.1), and the 1-, 2-, and 5-year survival rates were 92.6%, 75.6% and 47.2%, respectively. Overall, these results support the effectiveness of CP-D in treating recurrent EOC.

The superiority of clinical symptomatology and intradermal skin test over each other is a controversial issue when deciding on CP-D.^[14,16,20] In contrast to the 2001 Zannoti et al index study

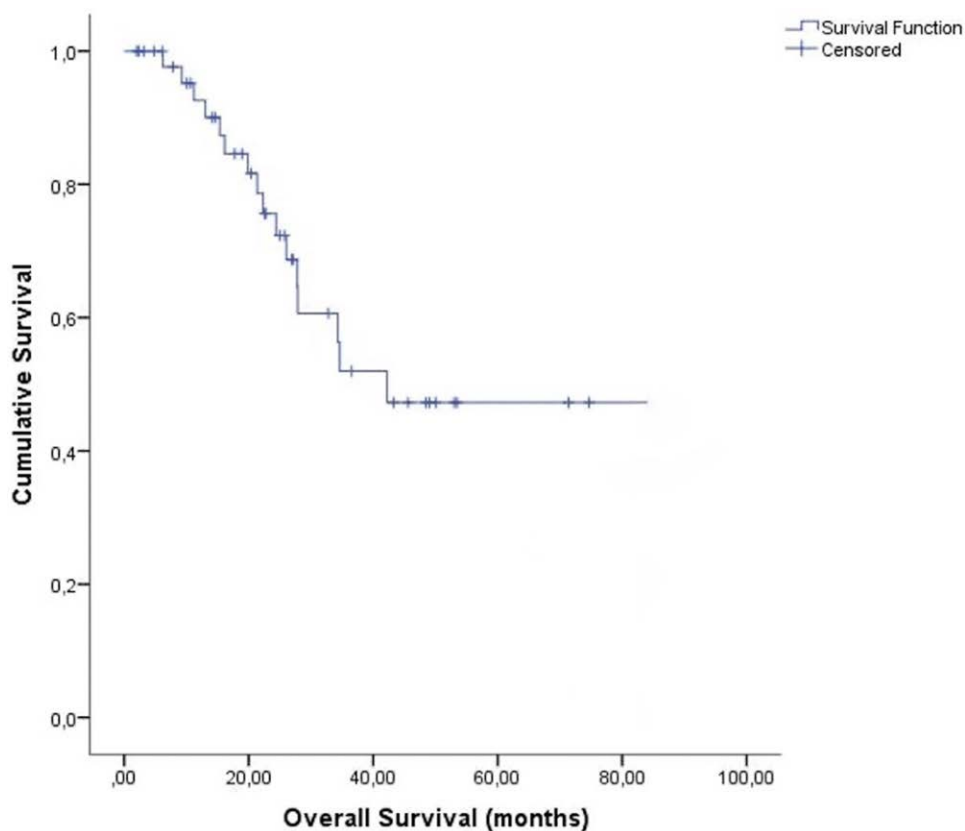


Figure 1. Survival curve of the start of carboplatin desensitization; median overall survival was 42.2 ± 8.6 mo (25.3–59.1 mo). The 1-, 2-, and 5-yr survival rates were 92.6%, 75.6%, and 47.2%, respectively.

Table 4
Responses to treatment and survival outcomes.

Variables	n = 47
Survival (95% CI)	
OS1, median (min–max)	121.3 months (72.2–170.4)
OS2, median (min–max)	42.2 months (25.3–59.1)
Best response to therapy	
Complete response, n (%)	12/25.4
Partial response, n (%)	25/53.1
Stable disease, n (%)	7/14.8
Progressive disease, n (%)	3/6.3
Objective response rate, n (%)	78.5
Disease control rate, n (%)	93.7

Table 5
Symptoms of carboplatin-induced HSR before and after desensitization.

	Before desensitization	During desensitization
Itching	29 (61.7%)	32 (68%)
Rash	25 (53.1%)	24 (51%)
Palmar erythema	22 (46.8%)	25 (53.1%)
Facial flushing	16 (34%)	17 (36.1%)
Shortness of breath, wheezing, bronchospasm	8 (17%)	5 (10.6%)
Angioedema	4 (8.5%)	2 (4.2%)
Hypotension	3 (6.3%)	1 (2.1%)
Anaphylaxis	3 (6.3%)	0
Death	0	0

HSR = hypersensitivity reaction.

showing the reliability of Carboplatin skin tests to predict HSR, various other authors reported false-negative rates as high as 8.5%. A carboplatin desensitization protocol can be used to prevent HSR in patients with a positive skin test or a history of HSR.^[10,11,14,15,20,21]

In our study, a total of 496 cycles of desensitization were performed in 47 patients, and 96.6% of them were successfully completed. However, 18 cycles were not completed. One patient experienced hypotension, and 5 patients developed respiratory symptoms. In such cases, rapid interventions were performed, and the infusion was interrupted first immediately. Fluid replacement, oxygen support, and steroid and antihistamine treatments were administered accordingly. As a result, his complaints were well-controlled without adrenaline, yet symptoms and hemodynamic findings were followed-up very closely with adrenaline ready to be used. No need for intensive care and no deaths due to desensitization were noted. Of the 18 dropouts, twelve were discontinued at the patients' request. In our study, the desensitization completion rate was similar to the 1 stated in previous studies.^[14–19]

This study has several limitations. First, its retrospective design may have led to biases in patient and treatment choices. However, it is essential to note that all patients were evaluated by the same physicians. Second, this retrospective clinical study was conducted on a heterogeneous patient population. However, unlike randomized trials with strict inclusion criteria, our findings may be more representative of patients observed in routine clinical practice.

5. Conclusions

Herein, we have presented real-life data on carboplatin desensitization treatment in platinum-sensitive recurrence EOC patients from a single institutional center. Based on our findings, we recommend carboplatin desensitization as an effective therapeutic approach with an acceptable safety profile for recurrent EOC patients.

This study was conducted in accordance with the tenets of the Declaration of Helsinki 1964. Retrospective analyses of clinical data were approved by the Academic Committee of the Istanbul University (File no: 2022/685254). The committee had agreed to the retrospective analysis of routinely collected clinical data without prior informed consent of patients.

Author contributions

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