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Prophylactic 3-hour graduated infusion schedule minimizes risk of carboplatin hypersensitivity reactions - A prospective study

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HIGHLIGHTS

- Low frequency of hypersensitivity reactions with graduated carboplatin infusion
- Benign nature of hypersensitivity reactions with graduated carboplatin infusion
- Appropriate premedication recommended with carboplatin retreatment

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ABSTRACT

Objective. Aim of this study was observation of hypersensitivity reaction (HSR) frequency by using a 3-hour graduated infusion protocol with appropriate premedication as a prophylactic measure in patients with gynecological cancer receiving carboplatin retreatment in second line or above. None of the patients had experienced HSRs to platinum previously.

Method. All the patients in this study received premedication with corticosteroids and anti-histamines followed by carboplatin as 3-hour graduated infusion. Carboplatin was administered either as monotherapy or in combination with other chemotherapeutic agents.

Results. Ninety-nine patients with ovarian ($n = 71$), fallopian tube ($n = 9$), peritoneal ($n = 9$) and other gynecological cancers (5 uterine cancer, 5 abdominal cancer of gynecological origin) were retreated by a total of 611 cycles of carboplatin administered as monotherapy (210 cycles) or combination regime (401 cycles). HSRs were recorded in only 11 cycles (1.8%) in a total of 11 patients. While 8 of these patients had grade 1or 2 reactions (8.1%), only 3 patients had grade 3 reactions (3%). After pause in the infusion and complete resolution of HSR symptoms, an attempt of retreatment using this infusion protocol with extra premedication was successful in 6 of these patients without any reoccurrence of HSRs.

Conclusion. In this prospective study, we report that prophylactic 3-hour graduated infusion rate with appropriate premedication is associated with low frequency of HSRs in gynecological cancer patients requiring carboplatin retreatment in second line or above.

1. Introduction

Platinum containing chemotherapy regimens are used in almost all gynecological cancers. These are not only the mainstay agents in the adjuvant therapy for epithelial ovarian (EOC) and related cancers, but also reportedly associate with higher response rates (30–75%) in the recurrence setting if the disease is considered platinum sensitive [1,2]. Carboplatin combination chemotherapy increases tumor response rates and prolongs progression free survivals in these patients [3]. The risk of hypersensitivity reactions (HSRs), however, increases with the repeated exposure to platinum drugs. During the first five cycles, the overall risk is <1%, rising to 6.5% with 6th cycle and reported to be as high as 27% in patients receiving more than seven cycles of treatment [4]. The overall incidence of carboplatin sensitivity may reach 100% in the third-line re-challenge setting [5]. Administration of cisplatin or oxaliplatin is an option in carboplatin sensitive patients, but given a risk of potential cross-reactivity, the administration requires a close supervision by experienced individuals who are prepared to deal with management of anaphylaxis [6–9]. Thus, for patients with platinum sensitive EOC, changing to a non-platinum chemotherapy in second line after HSRs may negatively impact quality of life and life expectancy. There are studies suggesting strategies to identify patients at risk to

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develop HSRs or preventing HSRs in individuals sensitized by platinum compounds. While skin test (ST) seems to be a promising method employed at centers providing collaboration between allergists and oncologists, there are indications of both a false negative and false-positive rate as well as risk of conversion to positivity with subsequent platinum exposure [10–13]. The long desensitization protocol method is highly efficacious and safe, but it is time consuming and expensive [14–17]. In a retrospective study, including 707 patients with platinum sensitive EOC and related cancers retreated with carboplatin over a 10-year period, O'Cearbhaill et al. concluded that fewer HSRs were recorded when the chemotherapy was administered as a prophylactic 3-hour graduated infusion compared to those receiving a standard 30-minute infusion (3% vs. 21%, $P = 0.001$) [18].

Aim of the present study was observation of HSR frequency, using the prophylactic 3-hour graduated infusion protocol with appropriate premedication in a prospective setting in patients with gynecological cancer receiving carboplatin retreatment in second line or above.

2. Material and methods

This prospective study was conducted at the Department of Hematology, Oncology and Radiation physics (gynecologic section), Skane University Hospital, Sweden, from May 2013 to May 2016. The ethical review board at the University approved the study (Dnr: 2016/549). All patients previously exposed to platinum and scheduled for carboplatin based chemotherapy in second line or above were considered for inclusion in this study. Other inclusion criteria were a histologically documented gynecological malignancy and platinum free interval (PFI) of at least 6 months. Patients with history of HSR to carboplatin or platinum agents were excluded. Clinical data of histological diagnosis, stage of disease and details of previous chemotherapy was easily retrieved from electronic journal system in the hospital. We examined previously reported risk factors for development of HSRs including age, history of allergy/atopy, relapse free interval after first line chemotherapy, PFI from last platinum containing chemotherapy, cumulative carboplatin dose before present chemotherapy, maximum carboplatin dose in present treatment, and type of chemotherapy given previously and in present line (carboplatin monotherapy or combination). Other parameters including extent of disease (limited to abdomen or generalized disease including liver metastases), body mass index (BMI), absolute glomerular filtration rate (GFR) estimated by iohexol clearance method, and CA-125 at the start of present treatment were also recorded (Table 1).

During the study period, patients received carboplatin either as monotherapy every three weeks (q3w) or in combination with either paclitaxel (175 mg/m^2, q3w), liposomal doxorubicin (40 mg/m^2, q4w) or gemcitabine (1000 mg/m^2 day 1 and 8, q3w). Carboplatin dose was calculated using Calvert formula, incorporating GFR estimations, for a target area under the curve (AUC) of 6 mg/mL per min in monotherapy regime and AUC 5 mg/mL per min in combination regimes. All patients were premedicated with 16 mg betamethasone orally evening before chemotherapy, and received intravenous administration of 16 mg betamethasone, 2 mg clemastine, 50 mg ranitidine and 8 mg ondansetron 30 min before chemotherapy infusion (in case of chemotherapy doublet, additional 2 mg clemastine was given 30 min before carboplatin infusion). The calculated dose of carboplatin for each patient was administered as 3-hour graduated infusion (1% of full dose over 1st hour, followed by 9% of full dose over 2nd hour and the remaining dose during 3rd hour) as according to the previously published protocol [15]. Patients were monitored carefully during and after carboplatin infusions. With development of HSRs, the infusion was stopped immediately. Necessary supportive care was administered and the patients were monitored until complete resolution of symptoms. All HSR symptoms, vital signs, grade of reaction, infusion rate at the time of HSR, exact time of HSR development from start of infusion, and requirement of hospitalization, if needed, were recorded. After the resolutions of symptoms, carboplatin re-challenge was tried same day in patients considered suitable for the procedure, depending upon their general condition and severity grade of HSRs (Table 2). These patients received extra premedication 30 min before restart of infusion with intravenous administration of 2 mg clemastine only or in combination with 1 mg lorazepam given orally in anxious patients.

Table 1
Demographic profile and descriptive analysis of patients.

Parameters	Without HSR[a] ($n = 88$)	With HSR ($n = 11$)
Age in years, median (range)	69 (35–89)	72 (58–82)
Primary cancer		
Ovarian cancer	65	6
Fallopian tube cancer	6	3
Peritoneal cancer	8	1
Others[b]	9	1
Stage of disease[c] (FIGO)		
I/II	7/10	0/1
III/IV	52/12	8/1
History of drug allergy/atopy	29/4	4/0
Median relapse free interval (range), mo[d]	18 (5–300)	16 (7–100)
Prior carboplatin cycles, median (range)[e]	6 (3–15)	6 (5–12)
Prior chemotherapy regimens (total cycles)[e]	601	71
Carboplatin only	60	12
Carboplatin/paclitaxel	474	59
Carboplatin/liposomal doxorubicin	6	0
Carboplatin/gemcitabine	14	0
Others[f]	47	0
Median cumulative carboplatin dose[e] (range), mg	3160 (978–6340)	3150 (1525–6150)
Median platinum free interval[g] (range), mo	16 (6–300)	13 (7–100)
Tumor limited to abdomen/distant metastases[h]	39/49	5/6
Median body mass index (range)[h]	25.8(17–47.8)	27.8(21.3–33.4)
Median absolute GFR (range)[h], ml/min	65.5 (32–126)	65 (27–90)
Median CA 125 (range)[h], units/ml	288(4–74,994)	91 (10–1389)
Present regime carboplatin cycles, median (range)	6 (1–18)	6 (2−12)
Present chemotherapy regimens (total cycles)	549	62
Carboplatin only	190	20
Carboplatin/paclitaxel	159	9
Carboplatin/liposomal doxorubicin	180	33
Carboplatin/gemcitabine	20	0
Median carboplatin dose present regime (range), mg	518 (258–800)	505 (215–576)
Disease status May 31, 2017		
Alive without disease	5	1
Alive with disease	28	1
Dead	55	9

[a] Hypersensitivity reactions.
[b] Uterus & abdominal cancer of gynecological origin ($n = 10$).
[c] Excluding stage X (non-operated; $n = 8$).
[d] First relapse in all patients.
[e] Prior to present regime.
[f] Carboplatin combined with cyclophosphamide, doxorubicin, docetaxel.
[g] Time since last platinum therapy.
[h] Start of present regime.

3. Results

A total of 99 patients with gynecological cancers were retreated with carboplatin during the study period. The median age of patients was 69 years (range 35–89). These included ovarian ($n = 71$), fallopian tube ($n = 9$), peritoneal ($n = 9$) and other gynecological cancers (5 uterine cancer, 5 primarily inoperable cancers of gynecological origin). The clinicopathological characteristics patients are listed in Table 1.

Most of the patients included in study had first recurrence of the disease (84 out of 99, 84.8%). These patients had received ≥1 lines (range 1–3) of chemotherapy, including a median of six (range 3–15) carboplatin cycles before the retreatment regime was administered in the study. Prior chemotherapeutic regimes were variable and consisted

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