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The anti-IgE monoclonal antibody omalizumab as adjuvant treatment in desensitization to carboplatin in patients with ovarian cancer

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1. Introduction

Ovarian cancer (OC) is the fifth most common cancer in women and the leading cause of death among gynecological malignancies, with a 5-year survival rate of 46% (Webb and Jordan, 2017). Primary treatment usually consists of appropriate surgical staging, followed in most cases by systemic chemotherapy where carboplatin (CP) plus paclitaxel represents the standard of care (Ozols et al., 2003; du Bois et al., 2003).

However, one of the main relevant concerns in using platinum-salts chemotherapy is the hypersensitivity reactions (HRs). Carboplatin-induced hypersensitivity reactions (CPHRs) have been registered in almost one third of patients (range 1–35%), (Markman, 2002; Sliesoraitis and Chikhale Carboplatin hypersensitivity, 2005). CPHRs have been more commonly detected in women who have been already exposed to CP-based chemotherapy in previous lines, reaching the highest incidence after an overall median number of seven cycles (Robinson et al., 2001). Indeed, patients having a platinum-sensitive ovarian disease have more than a 50% possibility to experience a CPHR when re-treated with CP at time of cancer recurrence (Schwartz et al., 2007). The onset timing of hypersensitivity ranges between few minutes (acute) and some hours or even days (late) after CP administration. Usually, a wide plethora of symptoms/signs from the mild-moderate such as skin rash, skin itching, facial flushing, dyspnea, chest pain, facial edema, chills, nausea, abdominal cramping, sweating, up to the severe life-threatening manifestations have been recorded.

The exact mechanism underlying the CPHRs is not completely known. However, a main role is played by IgE antibodies directed against CP that may be found in patients developing CPHRs (immediate type 1 IgE-mediated CHRs) (Iwamoto et al., 105 (2014),; Caiado et al., 1 (2013)). Drug desensitization (DD) is a procedure that allows temporary clinical tolerance to a drug, by administering its increasing amounts to complete the therapeutic dose. However, despite desensitization, some patients still undergo CPHRs (Markman, 2002). Although the majority of desensitization procedure are successfully and safely completed, a proportion of them may be complicated by breakthrough reactions, that can be observed more frequently at the last steps. We report three cases of OC patients experiencing a CPHR during a desensitization 16-steps protocol, in which the concentration in each successive solution increased by a factor of 10. An example of the protocol used in desensitization with carboplatin is summarised in Table 1 (Liu et al., 2011).

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Table 1
Desensitization Protocol for Carboplatin.

Steps	Solution	Rate (ml/h)	Time (min)	Volume infused (ml)/step	Dose administered (mg)/step	Cumulative dose (mg)
1	1	2.5	15	0.625	0.00125	0.00125
2	1	5	15	1.25	0.0025	0.00375
3	1	10	15	2.5	0.005	0.00875
4	1	20	15	5	0.01	0.01875
5	2	2.5	15	0.625	0.0125	0.03125
6	2	5	15	1.25	0.025	0.05625
7	2	10	15	2.5	0.05	0.10625
8	2	20	15	5	0.1	0.20625
9	3	5	15	1.25	0.25	0.45625
10	3	10	15	2.5	0.5	0.95625
11	3	20	15	5	1	1.95625
12	3	40	15	10	2	3.95625
13	4	10	15	2.5	5	8.95625
14	4	20	15	5	10	18.95625
15	4	40	15	10	20	38.95625
16	4	60	231	231	461.04375	500

The patients were then treated with anti-IgE monoclonal antibody (mAb) omalizumab which allowed them to safely complete CP chemotherapy schedule.

2. Case series

Case 1. *The case concerns a 60-year-old woman who had undergone bilateral hysteroannessiectomy, omentectomy and appendectomy for BRCA1-mutated high-grade serous ovarian cancer (HGSOC) in* 2017 (*FIGO stage IIIB*) (*see* Table 2). *Adjuvant chemotherapy with CP and paclitaxel for six cycles was performed.*

The patient was referred to our Hospital following the evidence of a platinum-sensitive pelvic relapse in December 2018. Since there was no indication for radical surgery, palliative chemotherapy with CP and gemcitabine was initiated in March 2019. During the first infusion of the 2nd cycle, despite optimizing premedication (dexamethasone 12 mg i.v. and chlorphenamine 10 mg i.v.) an HR occurred after 10 min from the start of CP administration. The reaction consisted of urticaria, dyspnea, hypotension and oxygen desaturation (sO2 86%). The patient was then treated with hydrocortisone 1 g i.v., chlorpheniramine 20 mg i.v. and oxygen support. During the allergological work-up, skin testing was performed and resulted positive for CP (IDT 1 mg/ml). The subsequent three administrations of CP were performed according to a 16-step DD protocol that were uneventful. However, the 4th DD was complicated by an HR, characterized by redness, urticaria, itching and throat constriction, requiring steroids and antihistamines i.v. Taking into account the positivity of skin testing suggesting an IgE-mediated reaction, a DD regimen with additional omalizumab was performed. Table 2 illustrates the timing and doses of omalizumab administration. The following three administrations were concluded without any HRs (June-July and August 2019). The patient reported a complete radiological and biochemical response to the chemotherapy and commenced maintenance treatment with Olaparib 6 weeks after the last cycle of CP. However, in May 2020, due to a hepatic relapse a further cycle of CP (6 administrations, every 3 weeks) was started (May 2020- October 2020). A breakthrough reaction during the second administration of this 3rd cycle at 9th step occurred, with hypertension, itching of hands and feet, chest discomfort. We then decided to start again omalizumab administration before each DD and in this manner additional four CP administrations were completed.

Case 2. *A 60-year-old woman with clear cell ovarian cancer (FIGO stage IIb) with no deleterious mutations of BRCA1/2 genes was treated with CP mono chemotherapy as adjuvant therapy in* 2017. *The patient completed six cycles without severe complications and was monitored every three months.*

Table 2
Summary of patients' characteristics and omalizumab protocol.

	Patient 1	Patient 2	Patient 3
Age (years)	60	60	76
Histology	HGSOC	Clear cell	HGSOC
Surgical debulking	Yes	Yes	Yes
BRCA status	Mutated	Wild-type	Wild-type
Atopy	No	no	Yes (Latex)
Treatment administered	Carboplatin	Carboplatin	Carboplatin
N° of drug administrations before HRs (total)	7	13	15
Clinical manifestations of initial HRs	Urticaria, dyspnea, hypotension, O2 desaturation	Flushing, malaise, vomiting, nausea	Flushing, chest discomfort, sweating
HRs Grade	3	2	2
Skin test	Positive (IDT 0.01 mg/ml)	Positive (IDT 0.1 mg/ml)	Negative
Details of breakthrough reactions	2nd DD, 9th step Urticaria, itching, flushing, throat constriction	2nd DD, 14th step Thoracic pain, nausea, vomiting, flushing, face angioedema	2nd DD, 8th step Urticaria, angioedema, flushing, throat constriction
Total serum IgE (UI/L)	925	NA	39.9
Dose of omalizumab	600 mg	600 mg	600 mg
Timing of omalizumab administration	−15 days and − 2 days Prior to the first optimized DD cycle, and then −2 days prior to each subsequent DD	15 days and − 2 days Prior to the first optimized DD cycle, and then −2 days prior to each subsequent DD	15 days and − 2 days Prior to the first optimized DD cycle, and then −2 days prior to each subsequent DD
N* of DD cycles successfully concluded	4	4	4
Adverse events to omalizumab	No	No	No

DD: drug desensitization; BRCA: breast related cancer antigen; IDT: intradermal test; FIGO: Federetion of Gynecology and Obstetrics; HGSOC: high grade serous ovarian cancer; HRs: Hypersensitivity reactions; NA: not available.

At 19 months from the end of chemotherapy, a computed tomography (CT) scan revealed hepatic disease recurrence not susceptible to surgical treatment. Having elapsed more than 12 months since the last administration of CP, we decided to treat the patient with CP, gemcitabine and bevacizumab for six cycles every three weeks, followed by bevacizumab as a single agent until disease progression. As elevated levels of Ca125 were found, a CT scan was performed and showed pelvic disease recurrence with multiple lymph node metastases, later confirmed by a Positron Emission Tomography (PET) examination. Because it had been 13 months since the end of the last administration, CP in association with paclitaxel was re-administered.

During the 1st administration of CP therapy (13th cycle in total), the patients experienced a mild reaction characterized by flushing, malaise, nausea, vomiting, occurring 20 min after the start of CP. Skin testing was positive to CP (IDT 0.1 mg/ml) and DD was performed for subsequent drug administration. The first procedure was uneventful; however, the second was complicated by a severe HR consisting of thoracic pain, nausea, vomiting, flushing and face angioedema. Blood examination revealed increase of troponin (36.6 pg/ml) and tryptase (from basal 6.1 to 29.4 pg/ml). Electrocardiography and echocardiographic evaluation did not show any alterations. CP treatment was continued by adding omalizumab to the subsequent DD procedures (Table 2). Omalizumab

was well tolerated, and the following four administrations of CP occurred without any side effects. A CT scan showed a partial response after the completion of 6th course of chemotherapy.

Case 3. *A 76-year-old female patient was diagnosed with HGSOC (FIGO stage IIIC), at the age of* 57 *and after adjuvant chemotherapy with paclitaxel and CP every three weeks for six administrations was performed. A second cycle (six administrations) of paclitaxel and CP were administered at the demonstration of pelvic recurrence six years later. During the follow-up, after another six years, an abdominal CT imaging revealed a peritoneal disease recurrence with the appearance of peritoneal metastases infiltrating the sigmoid colon and three iliac enlarged lymph nodes. A positron emission tomography examination showed a massive tracer uptake at the lesions described in the comparison CT. Therefore, in September* 2014 *six cycles of CP treatment were planned. Few minutes after the start of the* 3rd *administration of the* 3rd *cycle, flushing, sweating and chest discomfort occurred and CP administration was discontinued. Two months later, the patient underwent surgery with anterior resection of the rectum and pelvic lymphadenectomy. The histological examination tested positive for adenocarcinoma of ovarian origin, no known mutations in BRCA genes were found. In September* 2020, *the patient come to our attention due to the discovery of* 2 *small focal lesions at the surface of the liver identified at a follow-up CT scan, whose histological examination revealed omental localization of HGSOC. The patient underwent an allergological work-up, skin testing resulted negative, likely due to the long-time interval between the reaction and the allergological evaluation.*

Anyway, we decided to proceed with DD. The patient well tolerated the first DD, but a breakthrough reaction occurred during the second procedure. Although tryptase levels remain within range they showed a 2-fold increase (7.38 pg/ml) two hours after HRs in comparison with baseline (3.55 pg/ml) The addition of omalizumab guaranteed the possibility to conclude the remaining 4 DD procedures (see Table 2). In fact, the patients received four further administrations of CP with the procedure of desensitization adjuvanted with the use of omalizumab, and no breaktrough reactions occurred.

3. Discussion

In this study, we describe a case series of successful adjuvant use of omalizumab in CP desensitization, in three patients who had experienced a previous breakthrough reaction and showing skin test positivity for CP. The efficacy of omalizumab allow us to validate the IgE involvement in CP in our cases.

The choice to use omalizumab was suggested by the demonstration of an IgE-mediated mechanism of reaction in our three cases. In fact, omalizumab, an anti-IgE monoclonal antibody indicated in the treatment of severe allergic asthma and chronic urticaria, is able to block circulating free IgE and prevent their interactions with high-affinity IgE receptors (FcεRI) expressed by mast cells and basophils, thus limiting the release of mediators involved in allergic response. The capacity to dissociate pre-bound IgE from its cellular receptor represents a further omalizumab's mechanism of action useful in preventing the IgE-mediated mast cells degranulation involved in CPHRs of our case series (Maggi et al., 2018).

Omalizumab dosing in asthma is based on the patient's weight and total IgE, while in urticaria a fixed dose of 300 mg is used (Humbert et al., 2005; Maurer et al., 2013). Different from the other case reports describing the use of 300 mg omalizumab during DD to platinum compounds (Ojaimi et al., 2014; Oude Elberink et al., 2020), we have used the maximum doses prescribable in asthmatic patients (600 mg) regardless the total IgE and the patient's weight, in order obtain a complete IgE blocking. Of course, we cannot exclude a successful role of omalizumab also at lower doses as reported in other cases, but the optimal drug dosage is still an unsolved question. In the same way the timing of omalizumab schedule before the DD and the maintenance of omalizumab pretreatment during DD cycles are not exactly defined.

The patients here described had failed standard desensitization protocols, while no other reactions in any grade have been presented at the following cycles of chemotherapy, thus completing the chemotherapy program. Of note, is extremely important to guarantee to OC patients the completion of CP-based chemotherapy, in order to have access to maintenance phase with Poly (ADP) ribose polymerase (PARP) inhibitors if absence of disease progression. The management of OC patients has radically modified in the last years with the introduction of inhibitors into standard-of-care therapy. According to international guidelines, tumors regardless of homologous recombination deficiency (HRD) status, showing partial, complete response or stable disease for at least 12 months after first line platinum-based chemotherapy (defined as platinum-sensitive) should be candidate to maintenance therapy. PARP inhibitors, as maintenance therapy, have been demonstrated effective in prolonging progression free survival (PFS) in platinum-sensitive OCs in four phase III trials (SOLO-1, PAOLA-1/ENGOT-OV25, PRIMA/ENGOT-OV26 and VELIA/GOG-3005) (Mirza et al., 2020; Pujade-Lauraine et al., 2017; Kristeleit et al., 2017). Thus, omalizumab as adjuvant in DD allowed to overcome the CHRs issues and it means to positively affect the expectancy of life of these patients. Actually, two out of three patients are still in maintenance treatment with PARP inhibitors, showing a good disease control.

In conclusion, omalizumab may represents a promising therapeutic option in preventing IgE-mediated CP-induced HRs during troublesome DD. Different DD protocols are available, based on the number of bags, number of steps and final rate of infusions. The adjiuvant use of omalizumab in DD might allowed us to reduce the number of steps and increase the final rate of infusions, thus speeding up the procedure while maintaining the safety profile. Further study in a wider range of cases is needed to confirm this hypothesis.

Owing its mechanism of action, it will be interesting to understand how the immunomodulatory activity of omalizumab could interact with anti-tumor activity of chemotherapy in terms of long-term outcomes. Finally, the definition of the optimal dosage and duration of omalizumab pretreatment represents a future challenge to be addressed in controlled trials.

CRediT authorship contribution statement

Alessandra Vultaggio: Conceptualization, Data curation, Investigation, Project administration, Writing – original draft. **Maria Cristina Petrella:** Conceptualization, Data curation, Investigation, Project administration, Writing – original draft. **Federica Tomao:** Supervision, Writing – review & editing. **Francesca Nencini:** Investigation, Data curation, Writing – original draft, Writing – review & editing. **Valentina Mecheri:** Investigation, Data curation, Writing – original draft, Writing – review & editing. **Andrea Marini:** Investigation, Data curation, Writing – original draft, Writing – review & editing. **Margherita Perlato:** Investigation, Data curation, Writing – original draft, Writing – review & editing. **Emanuele Vivarelli:** Investigation, Data curation, Writing – original draft, Writing – review & editing. **Claudia De Angelis:** Investigation, Data curation, Writing – original draft, Writing – review & editing. **Ilaria Ferrarini:** Investigation, Data curation, Writing – original draft, Writing – review & editing. **Serena Pillozzi:** Supervision, Writing – review & editing. **Andrea Matucci:** Supervision, Validation. **Lorenzo Antonuzzo:** Supervision, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent section

written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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