



Analysis and treatment of 45 platinum-allergic gynecologic malignant tumors

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Abstract

Background This study aimed to explore the potential risk factors of platinum allergy and follow-up treatment to provide a reference for the clinical prevention and treatment of platinum allergic reactions in patients with gynecological tumors.

Methods The study retrospectively analyzed 45 cases of platinum allergic reactions that occurred in Shengjing Hospital affiliated to China Medical University from August 2010 to July 2016. Analysis of risk factors included the cumulative dose, treatment course and time intervals.

Results The cumulative carboplatin dose in allergic patients ranged from 900 to 10250 mg (average 4845 mg). The 45 allergic reactions occurred between the 3rd and 25th course of treatment (average 11.4 courses). The average re-treatment interval of carboplatin-allergic patients was 28.1 months, including 93.3% of patients with platinum re-treatment interval of more than 1 year. The allergic reaction occurred in the 2nd or 3rd course of re-treatment in 26 patients, accounting for 70.3% of all patients with recurrence. Seventeen patients were subjected to desensitization therapy, among which 13 cases were well tolerated.

Conclusions Patients who received more than 8 courses of carboplatin or a cumulative dose of more than 3500 mg were the high-risk population for platinum allergy. The 2nd and 3rd treatment course after restarting carboplatin treatment after an interval time of more than 1 year was the high incident period of carboplatin allergy. Skin tests should be conducted in patients with high risk of carboplatin allergy. In cases of carboplatin allergy, patients could receive carboplatin or oxaliplatin desensitization therapy.

Keywords Platinum allergy · Gynecologic malignant tumors · Desensitization therapy · High-risk scoring standard

Introduction

In recent years, the increased use of platinum-based drugs in clinical applications has increased the incidence rates of platinum allergy. Studies have reported the incidence rate of carboplatin allergy to be 1–44% [1–3], cisplatin allergy to be 5–20% [4] and oxaliplatin allergy to be 10–18.9% [5, 6]. Given the heavy use of platinum-based therapies for gynecological malignancies, gynecological oncologists should pay special attention to platinum allergy. We analyzed the

clinical features of 45 platinum allergy cases admitted in the gynecological oncology ward of Shengjing Hospital affiliated to China Medical University from August 2010 to July 2016, to develop a standard for evaluating and classifying patients according to risk factors of platinum allergy. We also analyzed prevention programs according to the evaluation score, providing a reference for the prevention and reduction of the risks of platinum allergy.

Patient and methods

The study included 45 patients aged between 34 and 71 years (mean 56.2 years), including 39 cases of ovarian cancer, 3 cases of fallopian tube cancer, 1 case of endometrial cancer, and 2 cases of cervical cancer. Among the 42 ovarian and fallopian tube cancer patients, 41 received satisfactory primary cytoreductive surgery and 6–8 courses of paclitaxel/

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docetaxel + carboplatin chemotherapy, 1 patient refused surgery. There were 50 episodes of allergic reactions in the 45 patients (Table 1).

Results

Clinical manifestations of allergic reactions

Among the 45 cases, allergic reactions in 37 patients appeared between 1 min to 2 h after chemotherapy initiation, with an average onset time of 28.2 min. In 19 cases (51.4%), the allergic reaction happened within 10 min. Allergic reactions were classified as mild (rash, itching, absence of change in vital signs), moderate (symptoms between mild and severe) and severe (blood pressure decrease, blood oxygen decrease, unconsciousness). The main symptoms included dyspnea, facial flushing, palpitations, itching, nausea and vomiting, blood pressure changes, blood oxygen decrease, rash, abdominal pain, hyperhidrosis, unconsciousness and dizziness (Table 2).

Emergency treatment

In the event of adverse allergic reactions, therapy was terminated immediately with application of a nasal catheter oxygen mask and monitoring of blood pressure, oxygen saturation and pulse, accompanied by rapid intravenous administration of saline and anti-allergic drugs (dexamethasone, methylprednisolone, epinephrine and other drugs), blood pressure elevation for hypotension patients (dopamine) and antispasmodic (aminophylline), sedation (diazepam and promethazine) treatment. All 45 patients were successfully rescued.

Treatment courses following platinum allergic reactions

Allergic reactions occurred during course 3–25, with an average of 11.4 ± 5.2 courses (median 10 courses), and those occurring at the 8th course or later accounted for 77.8% (35/45) of all reactions. Additionally, 82.2% (37/45) of cases occurred during treatment after recurrence, with patients experiencing allergic reactions at the 2nd or 3rd

Table 1 Cases and episodes of platinum allergic reactions

Classification	Carboplatin allergic reaction	Cisplatin allergic reactions	Oxaliplatin allergic reactions	Nedaplatin allergic reaction	Total
Cases	35	5	4	1	45
Episodes	38	5	6	1	50

Table 2 Clinical manifestations of allergic reaction

Symptoms	Cases	Percentage
Allergic shock	10	22.2
Dyspnea	21	46.7
Facial flushing	20	44.4
Palpitations	16	35.6
Itching	15	33.35
Blood pressure changes	14	31.1
Nausea and vomiting	13	28.9
Blood oxygen decrease	9	20
Rash	8	17.8
Abdominal pain	6	13.3
Hyperhidrosis	5	11.1
Unconsciousness	5	11.1
Dizziness	4	8.9

course of treatment after recurrence accounting for 70.3% (26/37) of all patients (Fig. 1).

Cumulative doses of platinum in patients

The cumulative dose of carboplatin in the 35 cases of allergy ranged from 900 to 10,250 mg with an average of 4845 ± 2019 mg (median 4500 mg), including 26 cases (74.3%) with a cumulative dose higher than 3500 mg. The 5 cases of cisplatin allergy, 4 cases of oxaliplatin allergy and 1 case of nedaplatin allergy showed reactions after platinum reuse due to tumor recurrence, the accumulated carboplatin dose of these patients ranged from 1500 to 6500 mg.

Time interval between treatments in recurrent patients

The time interval between treatments in the 37 recurrent patients ranged from 4.5 months to 11 years, with

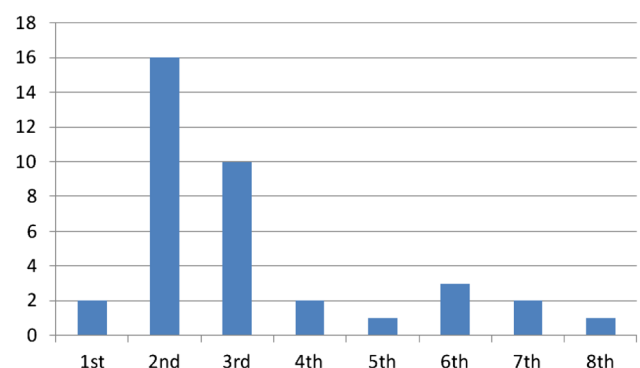


Fig. 1 The incidence of platinum allergy during treatment after recurrence

Table 3 Clinical features of platinum allergy

	Courses of platinum treatment	Cumulative platinum dose (mg)	Time interval before second platinum treatment (months)
Average	11.4 ± 5.2 courses	4845 ± 2019	28.1 ± 23
Median	10 courses	4500	20.5

Table 4 Platinum allergy score

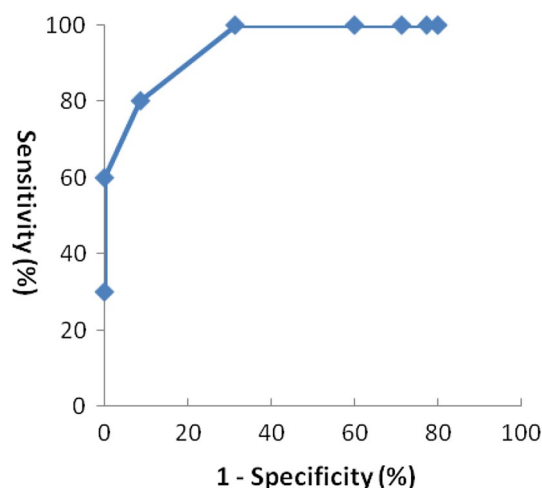
Score	Courses of platinum treatment	Cumulative platinum dose (mg)	Time interval before second platinum treatment (years)	Duration of second platinum treatment
0	< 8 courses	< 3500	< 1	Others
1	≥ 8 courses	≥ 3500	≥ 1	Third course
2	≥ 12 courses	≥ 8000	≥ 2	Second course

an average of 26.4 ± 21.7 months (median 19 months). Among them, the time interval for the 30 cases of carboplatin allergy ranged from 7 months to 11 years, with an average of 28.1 ± 23 months (median 20.5 months). The time interval for 93.3% of these cases (28/30) was more than 1 year, and was over 2 years for 46.7% (14/30) of those cases of carboplatin allergy. The clinical features of platinum allergy are described in Table 3.

Follow-up treatments for allergic patients

The symptoms of the first allergic reaction in four patients were mild and occurred at home. For these patients the allergic reaction after treatment restart/recurrence occurred earlier than the first time and with more serious symptoms, including 1 case of cardiac arrest, which was rescued by cardiopulmonary resuscitation (giving up treatment afterwards), and the other 3 cases were switched to non-platinum-based treatments.

Desensitization therapy was administered to 17 patients. The method of desensitization therapy refers to Mariana's study [7] and there were 2 cases each of carboplatin and cisplatin, who were successfully desensitized using the original scheme. One carboplatin-allergic patient failed during carboplatin desensitization, and then achieved successful desensitization using oxaliplatin. Nine carboplatin-allergic patients directly received oxaliplatin desensitization, which was successful in 5 cases, with the other 4 cases failed and were switched to a non-platinum regimen. There were one of each of oxaliplatin-, nedaplatin- and cisplatin-allergic patients who achieved successful desensitization of oxaliplatin. Among the remaining 24 patients, 2 completed more than 6 courses of first-line chemotherapy and achieved complete remission, 16 cases were switched to non-platinum-based regimes for continuous treatment, and the remaining 6 patients abandoned treatment.

**Fig. 2** ROC curve of platinum allergy score of 45 platinum-allergic patients

High-risk scoring standard and verification of platinum allergy

A high-risk scoring standard was determined according to the clinical features of the 45 patients with platinum allergy and the relevant literature reports. The highest score was set at 8 points, with 0–2 indicating low risk, 3–5 indicating moderate risk and 6–8 indicating high risk (Table 4).

The 45 cases of platinum-allergic patients were evaluated according to the scoring standard along with an analysis of their clinical symptoms. Ten patients were determined to be low-risk with no severe allergic reactions observed, 26 were determined to be at moderate-risk, with 15% (4 cases) manifesting severe allergic reactions and 9 patients were determined to be at high-risk, with severe allergic reactions occurring in 67% (6 cases) of these patients. The ROC curve may demonstrate the reliability of this scoring system (Fig. 2).

From August 2016 to March 2017, we performed a total of 344 carboplatin chemotherapy, there were 234 episodes of low-risk patients, 108 episodes of moderate-risk patients, and 2 episodes of high-risk patients. According to the degree of risk to take prevention, no patients developed severe allergic reactions.

Discussion

In 1975, cisplatin, the first-generation platinum-based therapy, was serendipitously found to inhibit bacterial growth and has since been gradually applied to the treatment of malignant tumors. Today, it is widely used and has achieved good curative effects in testicular, ovarian, bladder, head and neck cancer and other solid tumors [8]. After the publication of five major clinical trials of cervical cancer [9–13], concurrent cisplatin-based chemotherapy became the first-line therapy for advanced cervical cancer. However, since 1986, carboplatin, a second-generation platinum compound, has gradually replaced cisplatin in ovarian cancer treatment, due to its similar efficacy and lower toxicity [14]. Since the end of the last century, the combination of paclitaxel and carboplatin has been used as first-line therapy for ovarian cancer and is the preferred therapy for sensitive relapsed patients. Studies have shown that this scheme is not only effective for ovarian cancer, but also has curative effects for endometrial and cervical cancer [15–17], becoming the first-line chemotherapy for these two malignancies. Therefore, carboplatin application is extensive in the three major gynecological tumors. Oxaliplatin is a third-generation platinum compound, and the first-line therapy for many malignant tumors [18–20]. Since there is no cross-resistance between oxaliplatin and cisplatin, it has been gradually applied towards cisplatin-resistant recurrent ovarian cancer and has achieved satisfactory results [21]. In recent years, many clinical studies have also confirmed the efficacy of oxaliplatin in recurrent ovarian cancer [22–24]. With the increasing application of platinum-based drugs in gynecological malignancies, platinum allergic reactions have also gradually increased; therefore, understanding the risk factors of platinum allergy and identifying high-risk patients for early prevention is essential.

Risk factors for platinum allergy

Most studies regarding platinum allergy have reported that its risk is associated with: (1) previous treatment courses, (2) cumulative dose and (3) the interval time between reuse of platinum. The risk of platinum allergies gradually increases with increasing courses of medication. For example, Markman et al. reported that the allergic incidence rate for patients receiving carboplatin chemotherapy for the first

time during the first 5 cycles of treatment was less than 1%, increasing to 6.5% by the 6th course and as high as 27% in patients receiving more than 7 therapy cycles [25]. A preliminary study by Markman et al. found that the platinum allergy incidence rate in patients receiving more than 8 cumulative cycles was significantly increased, with the incidence rate in patients receiving 8 courses or more as high as 29.3% [2]. Koshiba et al. showed that the allergic rate in patients receiving 9 courses of carboplatin therapy was significantly increased, while the incidence rate of severe allergic reactions increased in patients receiving more than 15 courses of carboplatin treatment [26].

Analyzing these three factors in our patient cohort, we found that the average number of courses in the 45 platinum-allergic cases was 11.4 ± 5.2 courses (median 10 courses), with 77.8% of patients receiving more than 8 treatment cycles. Thus, in our final risk score 8 or more courses and 12 or more courses were set as thresholds for high risk. In addition, platinum allergic reactions are related to the cumulative dose of platinum. Wang et al. reported 13 cases of carboplatin allergy with cumulative dosages of 1900–1911,400 mg, and an average dosage of 4840 mg [27]. The cumulative dose of carboplatin in the allergic cases of this study ranged from 900 to 10,250 mg, with average cumulative dose of 4845 ± 2019 mg (median 4500 mg), and the allergic rate in patients with cumulative carboplatin doses over 3500 mg was 74.3%. Koshiba et al. showed that the risk of severe allergic reaction increases when the cumulative dose of carboplatin reaches 8000 mg [26]. Therefore, we used a cumulative carboplatin dose of 3500 or 8000 mg and higher as thresholds for high risk scoring. Finally, allergic reactions are associated with the interval of carboplatin treatment. Schwartz et al. reported that the incidence and severity of carboplatin allergy was correlated with the time interval of carboplatin treatment, with allergic rate of 25.8% in patients receiving less than 12 months of carboplatin treatment, and 56.5% in patients with a carboplatin treatment interval of more than 12 months [28]. The incidence rate of severe allergies also increases with longer treatment interval times. Gadducci et al. assessed 69 cases of allergic reactions in patients receiving carboplatin due to recurrent ovarian cancer, and the time interval in 15 cases (21.7%) was more than 2 years, which was regarded as the main factor for predicting the occurrence of allergic reactions [29]. Among the 30 carboplatin-allergic patients with cancer recurrence, the platinum treatment interval in 93.3% patients was longer than 1 year, and longer than 2 years in 46.7% patients. Therefore treatment intervals greater than 1 and 2 years before the second usage of platinum-based therapy were set as thresholds for the risk score.

In addition, we also found that the 2nd and 3rd courses of chemotherapy after recurrence were the high-risk period for platinum allergy, accounting for 70.3% of recurrent patients,

and that the incidence rate during the second course was higher than the third. Among the platinum allergic reactions in patients receiving carboplatin due to recurrent ovarian cancer reported by Gadducci et al., 86.7% of the allergic reactions occurred during the second course of chemotherapy, which was consistent with the report by Markman et al. [2, 29]. Therefore, the 2nd and 3rd courses of platinum reuse were set as risk factors.

Follow-up treatment after platinum allergic reactions

Platinum is the main treatment option for all three major gynecological malignant tumors. Thus, follow-up treatments for patients with platinum allergy are a challenge for clinicians. Desensitization therapy with dilution method to extend the drug infusion times after carboplatin allergic reaction has been reported in several clinical studies. Lee et al. utilized a 6-h 12-step desensitization scheme in 10 cases of carboplatin-allergic patients, with 35 courses of carboplatin desensitization treatment successfully completed including 31 treatment courses without adverse reaction [30]. Confino-Cohen et al. also reported a safe and effective 6-h desensitization treatment method in carboplatin-allergic cancer patients [31]. Choi et al. demonstrated that the effectiveness of carboplatin desensitization treatment is associated with treatment duration [32]. In this study, among the 12 cases of carboplatin-allergic patients, 3 cases received carboplatin desensitization therapy, which was successful in 2 cases. One failure and the other 9 cases of carboplatin allergy, and one of each of cisplatin and nedaplatin allergy were subjected to desensitization by oxaliplatin, among which 8 cases were well tolerated and completed the follow-up treatment; the other 4 cases were switched to a non-platinum-based regimen for follow-up treatment.

Although there were no cross-resistance reactions between oxaliplatin and carboplatin, there were cross-allergic reactions between oxaliplatin and carboplatin. However, in recent years, many researchers have tried oxaliplatin desensitization treatment in carboplatin-intolerant patients and succeeded. For example, Rose et al. retrospectively analyzed 281 patients receiving carboplatin chemotherapy, including 28 cases of carboplatin allergy (10%), which were then subjected to carboplatin desensitization therapy [33]. Among the 28 cases, 9 (29%) were switched to oxaliplatin desensitization due to intolerance of carboplatin desensitization, all of whom were able to tolerate oxaliplatin desensitization. Kolomeyevskaya et al. analyzed 46 patients with carboplatin allergy, among which 27 cases were given oxaliplatin treatment, and 19 were treated with cisplatin [34]. They concluded that oxaliplatin demonstrated better tolerance and longer effective time after carboplatin allergy. This begs the question, why do platinum-allergic patients have

better tolerance to oxaliplatin desensitization? The mechanism of platinum allergy is not clear, but most believe that it is a kind of type I allergic disease. The allergy specialists Caiado et al. evaluated the sensitivity and specificity of carboplatin-, cisplatin- and oxaliplatin-specific IgE (sIgE), and the results showed that carboplatin sIgE has a high specificity but lower sensitivity [35]. On the contrary, oxaliplatin sIgE demonstrated relatively high sensitivity and low specificity. The data analysis showed that exposure to oxaliplatin is more prone to immunogenicity, and thus most patients with carboplatin allergy can tolerate oxaliplatin. On the contrary, oxaliplatin allergic patients may produce more severe allergic reactions when exposed to cisplatin or carboplatin. Therefore, patients with failed oxaliplatin desensitization should be switched to non-platinum-based chemotherapies.

Strategies for preventing platinum allergy based on risk scoring

Clinicians now face more and more platinum allergies. Many researchers have tried to identify people with high risk of platinum allergy to prevent its occurrence. Gomez et al. analyzed carboplatin skin test results of 54 of patients treated with carboplatin chemotherapy, including 7 with positive results who were given carboplatin desensitization therapy, but allergy still occurred in 3 cases; among the 47 patients with negative skin test results, 4 demonstrated carboplatin allergy, yielding a false-negative rate of 8.5% [36]. The calculated results of carboplatin allergic skin test demonstrated a carboplatin allergy prediction sensitivity of only 64%, with a negative predictive value of 91%; while the specificity and the positive predictive value of both were 100%. These results demonstrate that a negative skin test is not absolutely reliable in predicting carboplatin allergic reactions. Moreover, the study by Hesterberg et al. showed that the carboplatin skin test results might be associated with the timing of tests [37]. Patients with no recent history of carboplatin allergy were still in the high-risk population of carboplatin allergy despite negative skin test results and demonstrated a high possibility of severe allergic reactions. We evaluated 45 cases of platinum allergy from our hospital and established a scoring standard based on high-risk factors of platinum allergy, along with an analysis of clinical symptoms. The results showed that there was no severe allergic reaction observed in low-risk patients, 15% of moderate-risk patients and 67% of high-risk patients developed severe allergic reactions. We propose that a routine risk score should be assigned to patients who will be treated with platinum, with prevention taken according to the proposed scoring system, which is likely to be more specific than skin tests. The probability of severe allergic reactions in low-risk patients is low, which can be handled by patient education.

For moderate-risk patients, in addition to patient education, platinum should be administered slowly at the beginning while monitoring blood pressure, oxygen saturation, and pulse, as well as observation in the first 30 min with standby rescue measures. Routine skin tests should be conducted in high-risk patients. Since patients with negative results may still develop allergic reactions, platinum should be administered slowly at the beginning, as well as observation closely. Patients with positive results should be subjected to a carboplatin desensitization program, if failed, it is recommended to switch to oxaliplatin desensitization program. From August 2016 to March 2017, we performed a total of 344 carboplatin chemotherapy; there were 234 episodes of low-risk patients, 108 episodes of moderate-risk patients, 2 episodes of high-risk patients. According to the degree of risk to take prevention, no patients developed severe allergic reactions. The value and significance of this classification should be verified by a larger study in the future. In addition, Iwamoto et al. examined CD203C basophilic cells and mean fluorescence intensity in 30 cases of gynecological tumor patients receiving carboplatin therapy [38]. The test results were analyzed along with the clinical symptoms of patients, and the results demonstrated that patients with allergic reactions had relatively high CD203C basophilic cell rate and/or elevated average fluorescence intensity, with particularly high expression level in patients with grade 4 allergic reactions, indicating that basophil CD203C cells may be a biomarker for severe carboplatin allergic reactions.

In conclusion, patients receiving more than 8 courses of carboplatin or a cumulative dose of more than 3500 mg are in the high-risk population for platinum allergy. Second, the 2nd and 3rd courses of platinum re-use with intervals longer than 1 year are the high incidence periods of platinum allergies. Third, patients with moderate or low risk of platinum allergy, patient education and close monitoring during medication is recommended to prevent platinum allergy; for high-risk patients, routine carboplatin skin testing is recommended, followed by a carboplatin desensitization program in patients with positive skin test results, patients with negative skin test results may still develop allergic reactions, platinum should be administered slowly at the beginning, as well as observation closely. Fourth, once carboplatin allergy occurs, carboplatin or oxaliplatin desensitization therapy can be employed for those with minor symptoms. Desensitization with carboplatin is not recommended for patients with more severe allergic reactions against carboplatin, while oxaliplatin desensitization could be considered. If oxaliplatin desensitization cannot be tolerated, continuous treatment with non-platinum drugs is recommended.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Morgan JS, Adams M, Mason MD (1994) Hypersensitivity reactions to carboplatin given to patients with relapsed ovarian carcinoma. *Eur J Cancer* 30A(8):1205–1206
2. Markman M, Kennedy A, Webster K et al (1999) Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* 17(4):1141–1145
3. Hendrick AM, Simmons D, Cantwell BM (1992) Allergic reactions to carboplatin. *Ann Oncol* 3(3):239–240
4. Koren C, Yerushalmi R, Katz A et al (2002) Hypersensitivity reaction to cisplatin during chemoradiation therapy for gynecologic malignancy. *Am J Clin Oncol* 25(6):625–626
5. Bautista MA, Stevens WT, Chen CS et al (2010) Hypersensitivity reaction and acute immune-mediated thrombocytopenia from oxaliplatin: two case reports and a review of the literature. *J Hematol Oncol* 3:12. <https://doi.org/10.1186/1756-8722-3-12>
6. Shibata Y, Ariyama H, Baba E et al (2009) Oxaliplatin-induced allergic reaction in patients with colorectal cancer in Japan. *Int J Clin Oncol* 14(5):397–401
7. Mariana C, Nichole M, David E et al (2008) Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 122(3):574–580
8. Williams CJ, Whitehouse JM (1979) Cis-platinum: a new anticancer agent. *Br Med J* 1(6179):1689–1691
9. Keys HM, Bundy BN, Stehman FB et al (1999) Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med* 340(15):1154–1161
10. Morris M, Eifel PJ, Lu J et al (1999) Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 340(15):1137–1143
11. Peters WA, Liu PY, Barrett RJ et al (2000) Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 18(8):1606–1613
12. Whitney CW, Sause W, Bundy BN et al (1999) Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol* 17(5):1339–1348
13. Rose PG, Bundy BN, Watkins EB et al (1999) Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 340(15):1144–1153
14. Alberts DS, Canetta R, Mason-Liddil N (1990) Carboplatin in the first-line chemotherapy of ovarian cancer. *Semin Oncol* 17(1 Suppl 2):S54–S60
15. Viswanathan AN, Moughan J, Miller BE et al (2015) NRG Oncology/RTOG 0921: a phase 2 study of postoperative intensity-modulated radiotherapy with concurrent cisplatin and bevacizumab followed by carboplatin and paclitaxel for patients with endometrial cancer. *Cancer* 121(13):2156–2163
16. Yang L, Guo J, Shen Y et al (2015) Clinical efficacy and safety of paclitaxel plus carboplatin as neoadjuvant chemotherapy prior to radical hysterectomy and pelvic lymphadenectomy for stage IB2-IIB cervical cancer. *Int J Clin Exp Med* 8(8):13690–13698

17. Symonds RP, Gourley C, Davidson S et al (2015) Cediranib combined with carboplatin and paclitaxel in patients with metastatic or recurrent cervical cancer (CIRCCa): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Oncol* 16(15):1515–1524
18. Souglakos J, Syrigos K, Potamianou A et al (2004) Combination of irinotecan (CPT-11) plus oxaliplatin (L-OHP) as first-line treatment in locally advanced or metastatic gastric cancer: a multicentre phase II trial. *Ann Oncol* 15(8):1204–1209
19. Giacchetti S, Perpoint B, Zidani R et al (2000) Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil–leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 18(1):136–147
20. Lee KH, Kim MK, Kim YH et al (2009) Gemcitabine and oxaliplatin combination as first-line treatment for advanced pancreatic cancer: a multicenter phase II study. *Cancer Chemother Pharmacol* 64(2):317–325
21. Chollet P, Bensmaïne MA, Brienza S et al (1996) Single agent activity of oxaliplatin in heavily pretreated advanced epithelial ovarian cancer. *Ann Oncol* 7(10):1065–1070
22. Bogliolo S, Cassani C, Gardella B et al (2015) Oxaliplatin for the treatment of ovarian cancer. *Expert Opin Investig Drugs* 24(9):1275–1286
23. Zhang G, Li XP, Liu BJ et al (2013) Oxaliplatin-based combination chemotherapy is still effective for the treatment of recurrent and platinum-resistant epithelial ovarian cancer: results from a single center. *Chin Med J (Engl)* 126(23):4477–4482
24. Vici P, Sergi D, Pizzuti L et al (2013) Gemcitabine-oxaliplatin (GEMOX) as salvage treatment in pretreated epithelial ovarian cancer patients. *J Exp Clin Cancer Res* 32(1):49. <https://doi.org/10.1186/1756-9966-32-49>
25. Markman M, Zanotti K, Kulp B et al (2003) Relationship between a history of systemic allergic reactions and risk of subsequent carboplatin hypersensitivity. *Gynecol Oncol* 89(3):514–516
26. Koshiha H, Hosokawa K, Kudo A et al (2009) Incidence of carboplatin-related hypersensitivity reactions in Japanese patients with gynecologic malignancies. *Int J Gynecol Cancer* 19(3):460–465
27. Wang HB, Shen K, Yang JX et al (2009) [Clinical analysis of thirteen cases of hypersensitivity reactions to carboplatin]. *Zhonghua Fu Chan Ke Za Zhi* 44(11):837–840 (**Chinese**)
28. Schwartz JR, Bandera C, Bradley A et al (2007) Does the platinum-free interval predict the incidence or severity of hypersensitivity reactions to carboplatin? The experience from Women and Infants' Hospital. *Gynecol Oncol* 105(1):81–83
29. Gadducci A, Tana R, Teti G et al (2008) Analysis of the pattern of hypersensitivity reactions in patients receiving carboplatin retreatment for recurrent ovarian cancer. *Int J Gynecol Cancer* 18(4):615–620
30. Lee CW, Matulonis UA, Castells MC (2004) Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. *Gynecol Oncol* 95(2):370–376
31. Confino-Cohen R, Fishman A, Altaras M et al (2005) Successful carboplatin desensitization in patients with proven carboplatin allergy. *Cancer* 104(3):640–643
32. Choi J, Harnett P, Fulcher DA (2004) Carboplatin desensitization. *Ann Allergy Asthma Immunol* 93(2):137–141
33. Rose PG, Metz C, Link N (2014) Desensitization with oxaliplatin in patients intolerant of carboplatin desensitization. *Int J Gynecol Cancer* 24(9):1603–1606
34. Kolomeyevskaya NV, Lele SB, Miller A et al (2015) Oxaliplatin is a safe alternative option for patients with recurrent gynecologic cancers after hypersensitivity reaction to Carboplatin. *Int J Gynecol Cancer* 25(1):42–48
35. Caiado J, Venemalm L, Pereira-Santos MC et al (2013) Carboplatin-, oxaliplatin-, and cisplatin-specific IgE: cross-reactivity and value in the diagnosis of carboplatin and oxaliplatin allergy. *J Allergy Clin Immunol Pract* 1(5):494–500
36. Gomez R, Harter P, Lück HJ et al (2009) Carboplatin hypersensitivity: dose introduction of skin test and desensitization reliably predict and avoid the problem? A prospective single-center study. *Int J Gynecol Cancer* 19(7):1284–1287
37. Hesterberg PE, Banerji A, Oren E et al (2009) Risk stratification for desensitization of patients with carboplatin hypersensitivity: clinical presentation and management. *J Allergy Clin Immunol* 123(6):1262–1267.e1
38. Iwamoto T, Yuta A, Tabata T et al (2012) Evaluation of basophil CD203c as a predictor of carboplatin-related hypersensitivity reaction in patients with gynecologic cancer. *Biol Pharm Bull* 35(9):1487–1495