



## Case report

# Sinus arrhythmia caused by pemetrexed with carboplatin combination: A case report

Xianghua Quan<sup>a</sup>, Haonan Zhang<sup>b</sup>, Wen Xu<sup>a</sup>, Mengna Cui<sup>a</sup>, Qie Guo<sup>a,\*</sup><sup>a</sup> Department of Clinical Pharmacy, The Affiliated Hospital of Qingdao University, China<sup>b</sup> Zibo City Zhangdian District People's Hospital, China

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## ABSTRACT

Combination chemotherapy of pemetrexed and carboplatin is a standard treatment approach for non-small cell lung cancer (NSCLC). However, no prior reports have described cardiotoxicity associated with this therapeutic combination or sinus arrhythmia in oncological contexts. Here, we report the case of a 44-year-old female NSCLC patient that suffered from sinus arrhythmia following combined chemotherapeutic treatment with pemetrexed and carboplatin. The patient was successfully treated under medical guidance, and the condition was effectively reversed following the discontinuation of this chemotherapeutic regimen and medication prescribing. Overall, this represents a rare case of sinus arrhythmia in NSCLC patient during the first cycle of combined chemotherapy with pemetrexed and carboplatin. However, a putative etiological basis for this rare clinical entity remains to be established.

## 1. Introduction

As a basic folate antagonist and antineoplastic agent, pemetrexed is primarily used to treat advanced non-small cell lung cancer (NSCLC) [1]. It alleviates rate-limiting enzyme activity in the folate-dependent metabolic pathway, inhibiting pyrimidine and purine biosynthesis from suppressing tumor cell proliferation [2]. Carboplatin is an intravenously administered platinum coordination complex and alkylating agent administered as a chemotherapeutic drug to treat lung cancer patients [3]. In many cases, pemetrexed and carboplatin are ideal for the chemotherapeutic treatment of NSCLC as they exhibit limited toxicity and significant chemotherapeutic efficacy [4]. However, herein we report the case of a patient who experienced sinus arrhythmia due to the combination therapy of pemetrexed and carboplatin.

### 1.1. Chief complaints

The 44-year-old female patient experienced paroxysmal palpitations without chest tightness and chest pain on the day of combined chemotherapeutic treatment with pemetrexed and carboplatin.

### 1.2. History of present illness

The patient received three cycles of combined chemotherapy of carboplatin and pemetrexed from August to October 2019; however, in the fourth cycle of chemotherapy, that is, around January 2020, the patient

developed cardiotoxicity. In particular, the patient suffered from sinus arrhythmia 8 h after the combined infusion of pemetrexed (800 mg q.d.) and carboplatin (450 mg q.d.).

### 1.3. History of past illness

The patient had no history of diabetes, hypertension, mental illness, or cardiovascular/cerebrovascular disease and did not receive any daily pharmacological treatment. However, the patient had been diagnosed with stage IV (cT4N1M1a) NSCLC, for that adenocarcinoma subtypes were identified since November 2011. Secondary malignant tumors in the bone and liver were also confirmed in this patient. Her medical schedule from 2012-2020 is detailed in Table 1.

### 1.4. Physical examination upon admission

An initial evaluation of the patient suggested her being underweight, with a body mass index (BMI) of 18.96 kg/m<sup>2</sup>, a temperature of 36.5 °C, blood pressure of 120/74 mmHg, and a heart rate of 121 bpm.

### 1.5. Laboratory investigations

Initial evaluations of patient electrolyte levels are illustrated in Supplementary Table 1. The complete blood count parameters do not show

\* Corresponding author.

E-mail address: [guoqie822a@qdu.edu.cn](mailto:guoqie822a@qdu.edu.cn) (Q. Guo).

**Table 1.** Medical history timeline for this patient.

2012.11–2013.11	Diagnosed with right lung adenocarcinoma with multiple metastases in both lungs (stage IV, cT4N1M1a).The patient was diagnosed EGFR gene mutation, and was administered with Gefitinib tablets. Patient underwent Cisplatin and Pemetrexed chemotherapy
2014.4	Progressive enlargement of the lower lobe of the right lung
2014.10–2015.11	Cisplatin and pemetrexed chemotherapy; Pemetrexed single drug maintenance
2015.12	Re-examination and evaluation: PD
2016.1	Cisplatin and pemetrexed chemotherapy; Synchronous intravenous pumping into ENDOSTAR
2016.3	Pemetrexed single drug maintenance; ENDOSTAR sequential therapy
2016.4	Pemetrexed single drug maintenance; ENDOSTAR sequential therapy
2018.4	Space occupying lesion of lower lobe of right lung with multiple metastases in both lungs
2018.5–12	Bevacizumab combined with Osimertinib targeted therapy was performed for 11 cycles. Allergic reactions to Bevacizumab occurred during the last round of chemotherapy
2019.2	MET mutation, oral Crizotinib, re-evaluated as PD after 1 month
2019.3	Orally Anlotinib hydrochloride
2019.4	Re-examination and evaluation: SD
2019.6	The patient suffered from pain in the right rib, and the pain worsened when lying down
2019.7	Cisplatin and Pemetrexed chemotherapy
2019.8	During chemotherapy, the patient developed an allergic response during the infusion of Cisplatin. Cisplatin was discontinued and Dexamethasone was administered (5 mg static push)
2019.8–2019.10	Pemetrexed and Carboplatin chemotherapy
2019.11	Reexamination and evaluation: PD
2019.12	Two-cycle (Paclitaxel Liposome for Injection) chemotherapy was performed; Zoledronic acid was administered for bone protection
2020.01	Pemetrexed and Carboplatin chemotherapy
2020.01	The patient suffered from sinus arrhythmia during chemotherapy. Due to the immediate onset of cardiotoxicity followed by chemotherapeutic treatment, the next dose of these chemotherapeutic drugs was suspended,
2020.01	Metoprolol Tartrate Tablets (12.5 mg b.i.d.) and Metoprolol Succinate Sustained-Release Tablets (47.5 mg q.d.); Regular ECG and UCG follow-up monitoring daily after sinus arrhythmia
2020.03	Intravenous infusion with Zoledronic acid (4 mg q.d.) and orally Ametinib (110 mg q.d.)

Abbreviations: PD: Progression Disease; SD: Stable Disease.

any abnormalities (Supplementary Table 1), while serum thyroxine (T4), triiodothyronine (T3), thyroid stimulating hormone (TSH), free T3 (FT3), and free T4 (FT4) levels were not assessed.

### 1.6. Imaging examinations

In light of the patient's high heart rate (121 bpm), she was assessed with a point-of-care electrocardiogram (ECG) monitoring within the first 12 h following presentation, revealing sinus tachycardia and marked sinus arrhythmia. Serum TroponinT (TnT), brain natriuretic peptide (BNP), creatine kinase isoenzyme (CKMB), and myoglobin (Myo) levels were analyzed, and no anomalies were found (Supplementary Table 2). Dynamic ECG results suggested frequent atrial premature beats and short-array chamber tachycardia. Ultrasound cardiogram (UCG) results were consistent with heart valve degeneration, aortic regurgitation, mitral regurgitation, tricuspid regurgitation, and impaired left ventricular diastolic function (Figure 1). Cardiologists were invited for consultation, and mild cardiotoxicity was specified for this patient.

### 1.7. Treatment

Due to the immediate onset of cardiotoxicity followed by chemotherapeutic treatment, the next dose of these chemotherapeutic drugs was suspended. Cardioprotective treatment was immediately initiated by administering *Metoprolol Tartrate Tablets* (12.5 mg b. i.d.). The patients presenting symptoms were alleviated after two days since such medication was initiated. However, she still experienced occasional palpitations, and dynamic ECG monitoring revealed paroxysmal sinus tachycardia and frequent atrial premature beats. Consequently, *Metoprolol Succinate Sustained-Release Tablets* (47.5 mg q. d.) were administered for six days. The patient underwent regular ECG and UCG follow-up monitoring daily after sinus arrhythmia.

### 1.8. Outcomes and follow-up

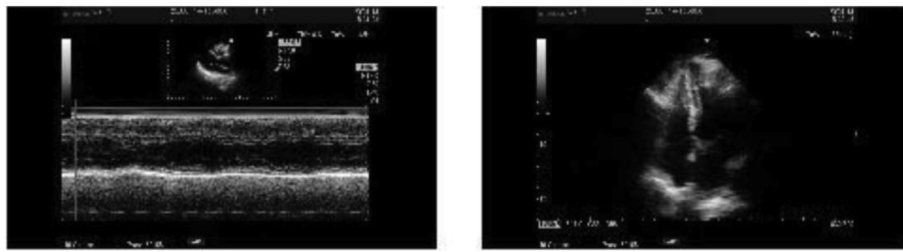
The patient exhibited occasional palpitations that disappeared after six days of the treatment of *Metoprolol Succinate Sustained-Release Tablets*, with ECG monitoring results returning to normal (Figure 2). Moreover, the chemotherapy with pemetrexed and carboplatin was suspended. The patient underwent intravenous infusion treatment with zoledronic acid (4 mg q.d.) and orally ametinib (110 mg q.d.).

### 1.9. Causality assessment

Naranjo adverse drug reaction algorithm was carried out to assess imputability resulting in a “probable” association [5]. Naranjo nomogram questionnaire yielded a score of 5, which contained the first evidence of a sinus arrhythmia induced by the combination of pemetrexed and carboplatin (Table 2).

## 2. Discussion

Cardiotoxicity rates range from 0.06% to 1.14% in patients undergoing antineoplastic drug treatment, with these adverse events primarily depending on the selected chemotherapeutic regimen, cardiac status, and drug dosage [6, 7]. 5-Fluorouracil (5-FU) and its precursor capecitabine have been reported to cause cardiotoxicity, presenting in the form of myocardial ischemia, arrhythmia, congestive heart failure, cardiogenic shock, and even sudden death [8]. However, such cardiotoxicity has primarily been attributed to frequent treatment and cumulative 5-FU administration [9]. Paclitaxel and carboplatin chemotherapy could induce abnormal ECG in ovarian cancer patients with either normal or abnormal prior ECG, but its consequence was of no clinical significance [10]. Nedaplatin-induced cardiotoxicity is also rare, although it has been presented that three patients treated with nedaplatin develop chemotherapy-induced serious arrhythmias [11]. In addition, few



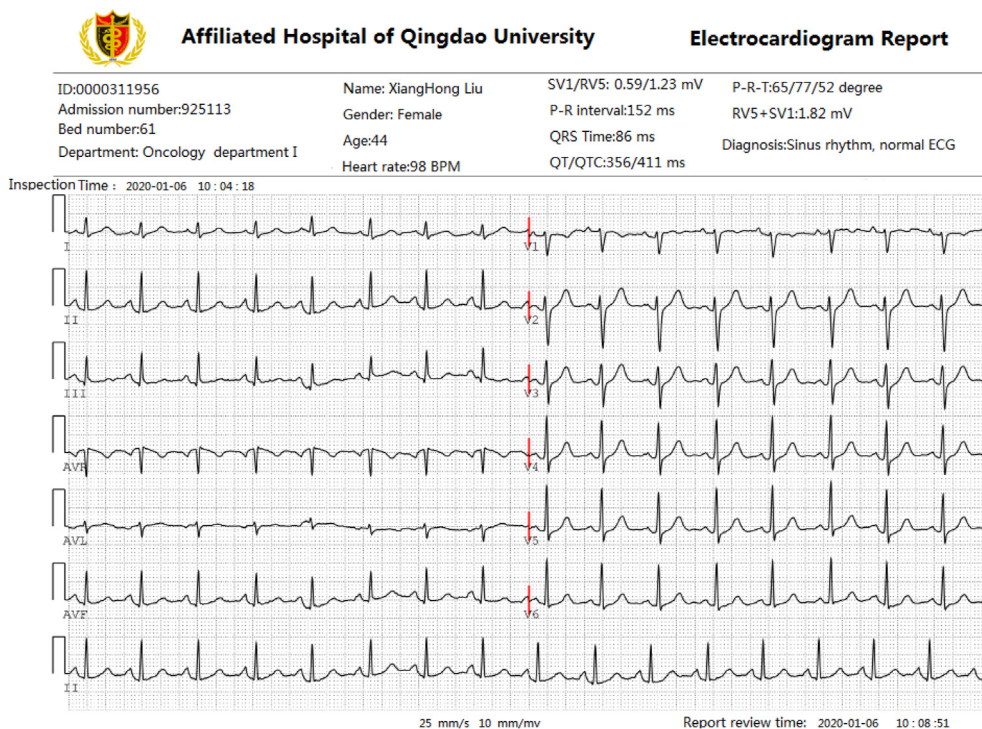
**Figure 1.** Ultrasound cardiogram definition for this paper. Ecdocardiography displaying heart valve degeneration, aortic regurgitation (mild), mitral regurgitation (mild), tricuspid regurgitation (mild), and impaired left ventricular diastolic function.

cardiac adverse effects have been observed on tyrosine kinase inhibitors (TKIs), although long-term erlotinib maintenance may have transformed minimal cardiotoxicity into dilated cardiomyopathy [12].

Pemetrexed is primarily metabolized in its original form and eliminated in the urine, causing limited damage to the renal system, peripheral nervous system, skin, and bone marrow [13]. However, there have been reports of pemetrexed-induced sweet syndrome and edema of the eyelids and scalp [14, 15]. Carboplatin is generally characterized as a relatively “gentle” chemotherapeutic drug, exhibiting limited hematopoietic toxicity [16]. Currently, no relevant evidence is available in findings about the cardiotoxicity induced by pemetrexed. Moreover, cardiotoxicity is not listed as a common side effect of platinum-based drugs, although the number of clinical cases reporting cardiotoxic events occurring during or shortly after cisplatin infusion has increased [17]. Most importantly, no patient-reported cardiotoxicity following the combination of pemetrexed and carboplatin was referred in clinical trials. The toxicity of neoadjuvant therapy was consistent with toxicity previously reported with pemetrexed/carboplatin, including neutropenia, anemia, myelosuppression and thrombocytopenia. Non-hematological adverse events such as febrile neutropenia, appetite loss, nausea, and bacterial pneumonia were rare [18, 19, 20, 21, 22, 23]. Here, we report a novel case in which pemetrexed and carboplatin appear to have triggered sinus arrhythmia in a patient undergoing multiple courses of chemotherapy. However, it is difficult to make any definitive statements regarding the mechanisms underlying this

case of sinus arrhythmia, given published evidence regarding the combination of pemetrexed and carboplatin treatment.

It has been hypothesized that cisplatin's cardiotoxicity occurs due to electrolyte imbalance or disturbance of the SA node [24]. Cisplatin is also speculated to direct ROS attacks on vascular endothelium, inducing platelet activation and aggregation to promote thrombosis [25]. Prior studies have reported sporadic instances of cardiotoxicity associated with antineoplastic drugs likely arising due to the induction of ischemia as a consequence of coronary artery spasms [26]. Herein, it is important to note that the patient did not exhibit sustained cardiotoxicity during the early stages of pemetrexed and carboplatin treatment, suggesting that the cumulative accumulation of these chemotherapeutic drugs for prolonged chemotherapeutic treatment is likely to have contributed to the development of sinus arrhythmia. UCG examination of the patient in the present report revealed evidence of heart valve degeneration, aortic regurgitation, mitral regurgitation, tricuspid regurgitation, and impaired left ventricular diastolic function. However, ECG results did not reveal the presence of any cardiovascular dysfunction before initiating the pem-carbo chemotherapy (Figure 3). Thus, it can be inferred that the accumulation of the selected chemotherapeutic drugs contributed to myocardial ischemia and sinus arrhythmia with concomitant impairments in cardiac energy metabolism, blood perfusion abnormalities, and oxygen deficiency. Secondary thrombosis due to damage to myocardial cells and the vascular endothelium may have occurred following chemotherapeutic treatment, contributing to

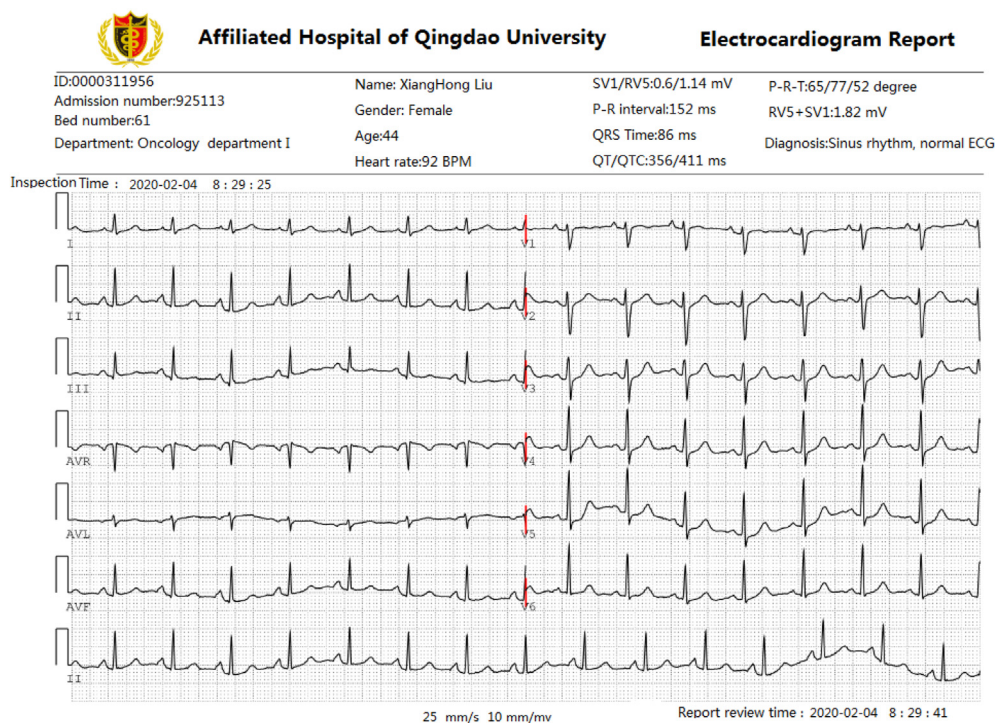


**Figure 2.** ECG monitoring for this patient.

**Table 2.** Naranjo Algorithm (NA) Assessment of adverse drug reaction (ADR) probability [5].

Component	Score			Total score
	Yes	No	DNK	
1.Are there previous conclusive reports on this reaction?	+1	0	0	0
2.Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3.Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4.Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	0
6.Did the reaction reappear when a placebo was given?	-1	+1	0	0
7.Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8.Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	+1
9.Did the patient have a similar reaction on the same or similar drugs in any previous exposure?	+1	0	0	0
10.Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
<b>Total Score</b>				<b>5</b>

Note: The probability that an adverse event is related to drug therapy was confirmed based on indicated questionnaire using the Naranjo criteria. A list of weighted questions such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose-response relationships and previous patient experience with the medication should be identified. The ADR is assigned to a probability category from the total score as follows:total score: >9 (Definite), 5–8 (Probable), 0–4 (Possible), and <0 (Doubtful). DNK: Do Not Know.

**Figure 3.** ECG monitoring before pem-carbo chemotherapy for this patient.

sinus arrhythmia. Additionally, it is important to consider that multiple factors, including cumulative chemotherapeutic drug accumulation, the selective cardiotoxicity of this chemotherapeutic regimen, aging, and heart disease-related risk factors, are likely to have all contributed to this case of sinus arrhythmia induced by the combination of pemetrexed and carboplatin.

To the best of our knowledge, this is the first published evidence suggesting that the combination of pemetrexed and carboplatin can induce cardiotoxicity. The present report of sinus arrhythmia in a patient undergoing combined pemetrexed and carboplatin treatment thus offers potentially new insight into the risk profile associated with this treatment regimen. However, it remains challenging to determine whether and how underlying cardiotoxicity in an otherwise asymptomatic patient was reinforced or exacerbated by these chemotherapeutic drugs. Further research exploring the mechanisms triggering sinus arrhythmia in patients undergoing combination pemetrexed and carboplatin-based

chemotherapy is thus warranted to elucidate the targeted solutions for these rare cases, even though the present patient exhibited an excellent outcome.

### Declarations

#### Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

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#### Data availability statement

Data included in article/supp. material/referenced in article.

#### Declaration of interest's statement

The authors declare no conflict of interest.

#### Additional information

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#### Patient consent

Informed consent was obtained from the patient.

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#### References

- [1] J.Y. Shih, A. Inoue, R. Cheng, R. Varea, S.W. Kim, Does pemetrexed work in targetable, nonsquamous non-small-cell lung cancer? A narrative review, *Cancers* 12 (2020) 2658.
- [2] G. Rossi, A. Alama, C. Genova, E. Rijavec, M. Tagliamento, F. Biello, et al., The evolving role of pemetrexed disodium for the treatment of non-small cell lung cancer, *Expert Opin. Pharmacother.* 19 (2018) 1969–1976.
- [3] L.E. Fox, Carboplatin, *J. Am. Anim. Hosp. Assoc.* 36 (2000) 13–14.
- [4] Y. Wang, S. Zou, Z. Zhao, P. Liu, C. Ke, S. Xu, New insights into small-cell lung cancer development and therapy, *Cell Biol. Int.* 44 (2020) 1564–1576.
- [5] C.A. Naranjo, U. Busto, E.M. Sellers, P. Sandor, I. Ruiz, E.A. Roberts, et al., A method for estimating the probability of adverse drug reactions, *Clin. Pharmacol. Ther.* 30 (1981) 239–245.
- [6] T. Kibby, A review of surface wipe sampling compared to biologic monitoring for occupational exposure to antineoplastic drugs, *J. Occup. Environ. Hyg.* 14 (2017) 159–174.
- [7] A. Bhagat, E.S. Kleinerman, Anthracycline-induced cardiotoxicity: causes, mechanisms, and Prevention, *Adv. Exp. Med. Biol.* 1257 (2020) 181–192.
- [8] Z. Sharalaya, P. Collier, Prevention of cardiotoxicities with traditional and novel chemotherapeutic agents, *Curr. Heart Fail. Rep.* 15 (2018) 260–269.
- [9] T. Shiga, M. Hiraide, Cardiotoxicities of 5-fluorouracil and other fluoropyrimidines, *Curr. Treat. Options Oncol.* 21 (2020) 27.
- [10] C. Kietpeerakool, J. Tiyyon, P. Suprasert, R. Kanjanavanit, J. Srisomboon, Benefit of electrocardiography during front-line combination paclitaxel and carboplatin chemotherapy for epithelial ovarian cancer, *J. Med. Assoc. Thai.* 89 (2006) 1805–1810. PMID: 17205858.
- [11] Y.J. Song, T. Fan, C.Y. Quan, S.H. Cao, Y. Zhang, X.H. Shao, Nedaplatin-induced arrhythmia: retrospective analysis of three cases, *J. Coll Physicians Surg Pak* 27 (2017) 657–659. PMID: 29056132.
- [12] F. Pinquie, G. de Chabot, T. Urban, J. Hureauux, Maintenance treatment by erlotinib and toxic cardiomyopathy: a case report, *Oncology* 90 (2016) 176–177.
- [13] T.A. Yap, J.G. Aerts, S. Papat, D.A. Fennell, Novel insights into mesothelioma biology and implications for therapy, *Nat. Rev. Cancer* 17 (2017) 475–488.
- [14] M. Korkmaz, M.K. Eryilmaz, M. Karaagaç, A. Demirkıran, M. Araz, M. Artaç, Pemetrexed-induced Sweet Syndrome: first case report in the medical literature, *J. Oncol. Pharm. Pract.* 27 (2021) 1307–1310.
- [15] M. Munera-Campos, A. Plana-Pla, J.M. Carrascosa, Pemetrexed-induced oedema of the eyelids and scalp in a patient with metastatic lung cancer, *J. Eur. Acad. Dermatol. Venereol.* 34 (2020) e322–e324.
- [16] J. Zhou, Y. Kang, L. Chen, et al., The drug-resistance mechanisms of five platinum-based antitumor agents, *Front. Pharmacol.* 11 (2020) 343.
- [17] R. Oun, Y.E. Moussa, N.J. Wheate, The side effects of platinum-based chemotherapy drugs: a review for chemists, *Dalton Trans.* 47 (2018) 6645–6653.
- [18] J.D. Hainsworth, D.M. Waterhouse, K.C. Shih, R.V. Boccia, V.M. Priego, M.J. McCleod, et al., Phase II trial of preoperative pemetrexed plus carboplatin in patients with stage IB–III nonsquamous non-small cell lung cancer (NSCLC), *Lung Cancer* 118 (2018) 6–12.
- [19] A. Ardizzoni, M. Tiseo, L. Boni, A.D. Vincent, R. Passalacqua, J. Buti S, et al., Pemetrexed versus pemetrexed and carboplatin as second-line chemotherapy in advanced non-small-cell lung cancer: results of the GOIRC 02-2006 randomized phase II study and pooled analysis with the NVALT7 trial, *J. Clin. Oncol.* 30 (2012) 4501–4507.
- [20] A. Lavole, L. Greillier, J. Mazières, I. Monnet, L. Kiakouama-Maleka, X.J. Quantin, et al., First-line carboplatin plus pemetrexed with pemetrexed maintenance in HIV-positive patients with advanced non-squamous non-small cell lung cancer: the phase II IFCT-1001 CHIVA trial, *Eur. Respir. J.* 56 (2020), 1902066.
- [21] N. Nogami, M. Nishio, I. Okamoto, S. Enatsu, K. Suzukawa, H.J. Takai, et al., Pemetrexed and carboplatin combination therapy followed by pemetrexed maintenance in Japanese patients with non-squamous non-small cell lung cancer: a subgroup analysis of elderly patients, *Respir. Investig.* 57 (2019) 27–33.
- [22] W. Kreisel, P. Deibert, L. Kupcinkas, J. Sumskiene, B. Appenrodt, S.J. Roth, et al., The phosphodiesterase-5-inhibitor udenafil lowers portal pressure in compensated preascitic liver cirrhosis. A dose-finding phase-II-study, *Dig. Liver Dis.* 47 (2015) 144–150.
- [23] M. Ito, N. Horita, A. Nagashima, T. Kaneko, Carboplatin plus pemetrexed for the elderly incurable chemo-naive nonsquamous non-small cell lung cancer: meta-analysis, *Asia Pac. J. Clin. Oncol.* 15 (2019) e3–e10.
- [24] R. Oun, E. Rowan, Cisplatin induced arrhythmia; electrolyte imbalance or disturbance of the SA node? *Eur. J. Pharmacol.* 811 (2017) 125–128.
- [25] S. Patané, Cardiotoxicity: cisplatin and long-term cancer survivors, *Int. J. Cardiol.* 175 (1) (2014) 201–202.
- [26] X. Zhang, Y. Zhu, S. Dong, et al., Role of oxidative stress in cardiotoxicity of antineoplastic drugs, *Life Sci.* 232 (2019), 116526.