Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Volume 10 Issue 2
MAY-AUG 2021
10.5281/zenodo.5381311

A CAUSAL RELATIONSHIP OF ANTICANCER DRUGS WITH SPECIFIC ARRHYTHMIAS

Ergashov Bobir Bahodirovich

Bukhara state medical institute, Bukhara, Uzbekistan

Abstract. Cardiotoxicity is a widespread complication of anticancer therapy. One of the most difficult manifestations of cardiotoxicity is cardiac arrhythmias. The incidence of arrhythmias in cancer patients has not been fully established because most studies had insufficient number of patients. Establishing a causal relationship between anticancer drugs and specific arrhythmias also presents certain difficulties. The purpose of this review is to analyze the modern data on the incidence and clinical course of arrhythmias in patients taking anticancer therapy.

Keywords: cardiovascular toxicity, anthracyclines, anticancer therapy, arrhythmias.

INTRODUCTION

The incidence of arrhythmias in cancer patients has not been precisely established, since patients with malignant neoplasms (MNO) were excluded from most studies. Establishing a causal relationship between anticancer drugs and specific arrhythmias also presents certain difficulties. First of all, the oncological disease itself can cause the development of arrhythmias. One of these arrhythmias is atrial fibrillation (AF), which develops against the background of chronic inflammation and metabolic disorders accompanying tumor processes [1, 8, 17, 21].

In addition to arrhythmias, anticancer drugs can also contribute to various changes in the electrocardiogram (ECG), such as prolongation of the corrected QT interval (QTc) and conduction disturbances. QTc lengthening is most often associated with exposure to potassium channels and the fast component of the delayed potassium rectifier IKr [9]. While QTc prolongation is a common side effect for many anticancer drugs, the incidence of life-threatening ventricular arrhythmias such

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Volume 10 Issue 2
MAY-AUG 2021
10.5281/zenodo.5381311
as torsades de pointes is low. Despite the rarity, the clinical consequences of such arrhythmias are extremely important, given their life-threatening nature [1, 4, 8, 10].

The lack of careful monitoring of the rhythm before, during and after chemotherapy complicates the identification of pre-existing arrhythmias and the assessment of the exact effect of anticancer drugs on the development and maintenance of rhythm disturbances.

The purpose of this review article is to analyze modern literary sources on the frequency of development and features of the course of arrhythmias arising against the background of anticancer therapy of oncological diseases.

Anthracyclines

Anthracyclines are commonly used to treat acute leukemias, lymphomas, and solid tumors in children and adults. Cardiomyopathy (CMP) is the most common manifestation of anthracyclines cardiotoxicity, but anthracyclines can also often cause primary and secondary arrhythmias. CMP associated with the use of anthracyclines occurs in 5-8% of cases and is most often due to the use of a high cumulative dose of the drug, amounting to> 450 mg / m2 with simultaneous radiation therapy and 550 mg / m2 without radiation therapy for doxorubicin and> 900 mg / m2 for epirubicin.

Anthracyclines suppress the function of Ca2 + -ATPase of the sarcoplasmic reticulum, disrupting the regulation of the intracellular level of Ca2 +. Their use can also disrupt the work of type II calmodulin kinase (CaMK11), which plays an important role in the regulation of ion channels such as L-type calcium currents (ICa) and fast sodium currents (INa). Both mechanisms of the cardiotoxic effect of anthracyclines can contribute to the development and maintenance of various arrhythmias. QTc lengthening is also characteristic of anthracyclines, with QTc> 450 ms observed after the first course of chemotherapy in 11.5% of patients [2, 3, 5, 11]. Severe QTc prolongation sometimes leads to life-threatening ventricular arrhythmias such as torsades de pointes, which quickly develop into ventricular fibrillation (VF).

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Volume 10 Issue 2
MAY-AUG 2021
10.5281/zenodo.5381311
Studies using 24-hour Holter ECG monitoring have shown an association between the administration of anthracyclines and the development of various arrhythmias, including sinus bradycardia and tachycardia, supraventricular premature beats (SVES) and ventricular premature beats (VES), supraventricular tachycardia (VVT) and gastric tachycardia (VAT) and gastric tachycardia (VT) and gastric tachycardia. During the first course of therapy, arrhythmias were found in 65% of patients. AF is a fairly common complication of anthracyclines and occurs in 10% of patients.

In a study by Numico G, et al. AF paroxysms were reported in 6.9% of 393 patients during the first course of chemotherapy with doxorubicin [6, 9, 10, 12].

Alkylating agents

Cyclophosphamide is widely used to treat breast cancer, lymphomas, leukemia, and multiple myeloma. Arrhythmias are one of the most common manifestations of cyclophosphamide-induced cardiotoxicity. A wide range of arrhythmias have been reported in patients treated with cyclophosphamide, including NSAIDs and VEBs, SVT, AF, ventricular arrhythmias with preceding lengthening of the QTc interval, and varying degrees of atrioventricular (AV) blockade.

Melphalan is an alkylating agent used to treat multiple myeloma, primary amyloidosis, and ovarian cancer. Arrhythmias are one of the most common side effects of treatment with melphalan, with AF occurring in 6.6-22.5% of patients [13, 14]. In a database of 438 patients who received high doses of melphalan after bone marrow transplantation, supraventricular arrhythmias, including AF and SVT, were observed in 11% of patients, while with other chemotherapy regimens, the incidence of arrhythmias was only 0 to 2% [7, 15, 18, 20].

Busulfan is another nonspecific alkylating agent used before bone marrow transplantation for leukemia, which is also associated with AF, with a frequency of ~ 6.4% when used in combination with cyclophosphamide [16, 22].

Antimetabolites

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Volume 10 Issue 2
MAY-AUG 2021
10.5281/zenodo.5381311

5-fluorouracil is often used for head and neck tumors as well as gastrointestinal and breast cancer. Arrhythmias are the second most common manifestation of 5-fluorouracil cardiotoxicity after acute coronary heart disease (IHD). Supraventricular arrhythmias are rare in patients receiving 5-fluorouracil monotherapy. In contrast, 5-fluorouracil can cause a wide range of ventricular arrhythmias from frequent VEBs to sudden cardiac death (SCD) in the presence of VT or VF [17]. The incidence of VT can reach 3.7-7.4% and often occurs in conditions of acute myocardial ischemia against the background of spasm of the coronary arteries.

Antimetabolites

It should be noted that vasospastic angina developed both in patients with previous coronary artery disease and in patients with normal coronary arteries, and was associated with spasms of the coronary arteries during treatment with these drugs [17]. Ischemia most often occurs after the 2nd or 3rd injection of the drug, for the treatment and prevention of which nitroglycerin and calcium channel blockers are successfully used. 5-fluorouracil can also cause sinus bradycardia in ≤11.96% of patients in addition to AV block and intraventricular conduction delays [9, 18].

Gemcitabine is used to treat bladder, pancreatic, non-small cell lung, ovarian, and cervical cancers. Its use is most commonly associated with the development of AF. The association of gemcitabine with AF is quite pronounced and may occur even after the first dose. In a series of 49 patients treated with a combination of gemcitabine and vinorelbine, AF occurred in 8.2% of patients [11, 19].

Clofarabine is an approved drug for the treatment of acute lymphoblastic leukemia. The most common arrhythmia associated with clofarabine treatment is also AF. The incidence of AF with the use of clofarabine ranges from 7.4% to 19%, depending on the treatment protocol and whether it is used as monotherapy or in combination with cytarabine [20, 21].

Anti-microtubule agents

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Volume 10 Issue 2
MAY-AUG 2021
10.5281/zenodo.5381311

Paclitaxel is an antineoplastic agent widely used to treat breast, ovarian, lung and cervical cancer. The most common arrhythmia associated with paclitaxel use is sinus bradycardia, which occurs in 29% of patients when paclitaxel is used as monotherapy, and even more often in combination with cisplatin. Sinus bradycardia is usually mild, transient, and asymptomatic. Rare cases of transient AV block have also been reported.

Platinum compounds

Cisplatin is widely used in the treatment of multiple cancers, including metastatic gonadal tumors and advanced bladder cancer. Often used as a drug for perioperative chemotherapy. Can be used systemically or for intracavitary administration. Systemic use of cisplatin is often associated with sinus bradycardia, which can begin immediately during infusion. Also common are NZHES and VES, AF and VT, caused by hypomagnesemia, which develops on the background of cisplatin infusion.

Cisplatin can be delivered locally by injection into the serous cavity. When used intraperitoneally, the risk of developing AF ranges from 12 to 18.8%. The risk of developing AF is even higher (23.9-66%) if a hyperthermic solution is used for instillation into the abdominal and pleural cavities in patients undergoing pleurectomy [13, 23].

Proteasome inhibitors

Bortezomib is used to treat multiple myeloma and mantle cell lymphoma. Heart failure is the most common manifestation of bortezomib-associated cardiotoxicity and can lead to secondary arrhythmias. Isolated cases of NVT and AF have been reported with bortezomib. Bradyarrhythmias have been reported rarely, including complete AV block, requiring permanent pacemaker implantation [10].

Targeted therapy (kinase inhibitors) Alektinib is approved for the treatment of metastatic non-small cell lung cancer. Bradycardia is the most common cardiac side

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Volume 10 Issue 2
MAY-AUG 2021
10.5281/zenodo.5381311
effect of alectinib, reported in clinical trials in 7.9% of patients, with sinus bradycardia reported in 5.1% of these [12].

Ceritinib inhibits anaplastic lymphoma kinase and is used to treat advanced or metastatic non-small cell lung carcinoma. May cause sinus bradycardia and prolongation of the QTc interval [23].

Crisotinib is an anaplastic lymphoma kinase inhibitor used to treat advanced or metastatic non-small cell lung carcinoma. The use of crizotinib is associated with the development of sinus bradycardia and prolongation of the QTc interval. According to two large multicenter retrospective studies PROFILE 1005 and 1007, the average observed decrease in heart rate in one series of patients was ~ 25 beats / min, while in 31% of patients the heart rate decreased <50 beats / min [14, 15].

Ibrutinib is a Bruton's kinase inhibitor used to treat chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenstrom's macroglobulinemia. The use of ibrutinib is often associated with the development of AF, which appears to be the primary arrhythmia. A recent meta-analysis found the relative risk of AF to be 3.86 (95% CI 1.97-7.54). The incidence of AF in clinical trials ranged from 5 to 7% with a mean time to onset of 3.0 to 3.8 months. after starting ibrutinib and 76% of cases occurring during the first year of therapy [17]. The risk of developing AF occurs early, continues to increase with therapy, and may persist for ≤2 wk. after you stop taking ibrutinib. The clinical implications and optimal treatment of AF in these patients are unclear. In a retrospective analysis of 56 cases of ibrutinib-induced arrhythmias, AF was persistent in 63% of patients despite treatment. The development of AF required complete withdrawal of ibrutinib in 46% of cases. Ibrutinib also increased the risk of bleeding in these patients, with 14% of non-thrombocytopenic AF patients experiencing major bleeding during treatment, which necessitated discontinuation of anticoagulants [16, 17].

Monoclonal antibodies

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Volume 10 Issue 2
MAY-AUG 2021
10.5281/zenodo.5381311

Trastuzumab is used in the treatment of breast and stomach cancers with tumor overexpression of HER2. The most common manifestation of trastuzumab cardiotoxicity is CMP, which in most cases is reversible with discontinuation of the drug. Rare cases of malignant ventricular arrhythmias have been reported, usually secondary to left ventricular systolic dysfunction [14].

Rituximab is used for adult B-cell non-Hodgkin lymphomas. Its use can be accompanied by severe heart failure with the development of symptoms weeks after the start of treatment. The infusion should be discontinued if life-threatening arrhythmias develop. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent rituximab infusions. However, it should be noted that the listed complications are quite rare [14].

Immunotherapy

Much attention is currently attracting to itself immunotherapy, which makes it possible to effectively treat a number of oncological diseases. At the same time, one of the serious complications of immunotherapy are autoimmune myocarditis, which can cause the development of acute heart failure and life-threatening arrhythmias against the background of a sharp decrease in myocardial contractility [15, 19].

Pembrolizumab is a human monoclonal antibody that selectively blocks the interaction between the programmed death receptor (PD-1) and its ligands PD-L1 and PD-L2, approved for the treatment of hepatocellular carcinoma, recurrent or metastatic cervical cancer when PD-L1 is expressed (CPS $\geq$ 1), classic Hodgkin's lymphoma, non-small cell lung carcinoma, malignant melanoma, and squamous cell carcinoma of the head and neck. Since this is a relatively new drug, the exact frequency of arrhythmias associated with it is unknown. Autoimmune myocarditis is the most common variant of cardiotoxicity associated with pembrolizumab. With its use, rare cases of sinus tachycardia with ventricular bigeminia, AF and SCD have been reported, which are probably secondary to autoimmune myocarditis [15, 18].

CONCLUSION

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Volume 10 Issue 2
MAY-AUG 2021
10.5281/zenodo.5381311

Modern schemes of chemotherapy and targeted therapy have led to an improved prognosis in patients with malignant neoplasm, however, the consequence of their use is cardiotoxicity, manifested not only by heart failure, but also by various arrhythmias. For cardiologists and arrhythmologists working with cancer patients, it is important to know the relationship of individual chemotherapeutic agents with specific arrhythmias for their early detection, prevention, and effective treatment. With the advent of new multicomponent treatment regimens, these tasks are becoming more and more complex.

Sinus bradycardia and tachycardia, as well as NSAIDs, which are a frequent complication of many anticancer drugs, do not pose a threat to life and do not require discontinuation of chemotherapy treatment. With poor tolerance and frequent episodes of NZhES or SAT, sinus tachycardia, it is possible to prescribe drugs of the group of beta-blockers or ivabradine, against which in most cases the rhythm can be normalized. These rhythm disturbances most often disappear against the background of dose reduction or discontinuation of chemotherapy.

Currently, the information on effective prevention of cardiotoxicity of chemotherapy is limited and concerns mainly the prevention of cardiac damage during therapy with anthracyclines or trastazumab. In these studies, a cardioprotective effect was demonstrated in bisoprolol, nebivolol, carvedilol and angiotensin-converting enzyme inhibitors.

References

1. Matskeplishvili ST, Potievskaya VI, Popovkina OE, et al. Cardiovascular complications of oncology treatment (cardiooncology): prevention, diagnosis, treatment — the consensus of experts. Technologies of living systems. 2018;15(6):3-35. (In Russ.)

2. Akhmedova N.Sh., Ergashov B.B., Nuralieva H.O., Safarova G.A. Influence of collected modified risk factors on the development and progression of chronic kidney

disease // International Journal of Current Research and Review Vol 13 • Issue 02 • January 2021 P. 13-17

3. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC committee for practice guidelines. Russ J Cardiol. 2017;(3):105-139. (In Russ.)

4. Krikunova OV, Vasyuk YA, Viskov RV, et al. Chemotherapy cardiotoxicity screening with cardiac troponins. Russian J Cardiol. 2015;(12):119-25. (In Russ.)
нал. 2014;(5):75-80. doi:10.15829/1560-4071-2014-5-75-80.

5. Snegovoj AV, Vicenya MV, Kopp MV, Larionova VB. Practice guidelines on correction of cardiovascular toxicity induced by chemotherapy and targeted agents. Zlokachestvennye opukholi.2016;418-27. (In Russ.)

6. Mazur M, Wang F, Hodge DO, et al. Burden of cardiac arrhythmias in patients with anthracycline-related cardiomyopathy. JACC Clin Electrophysiol. 2017;3(2):139-50. doi:10.1016/j. jacep.2016.08.009

7. Diwadkar S, Patel AA, Fradley MG. Bortezomib-induced complete heart block and myocardial scar: the potential role of cardiac biomarkers in monitoring cardiotoxicity. Case Rep Cardiol. 2016;2016:3456287. doi:10.1155/2016/3456287.

8. Morcos PN, Bogman K, Hubeaux S, et al. Effect of alectinib on cardiac electrophysiology: results from intensive electrocardiogram monitoring from the pivotal phase II NP28761 and NP28673 studies. Cancer Chemother Pharmacol. 2017;79(3):559-68. doi:10.1007/s00280-017-3253-5.

9. Ou SH, Tang Y, Polli A, et al. Factors associated with sinus bradycardia during crizotinib treatment: a retrospective analysis of two large-scale multinational trials (PROFILE 1005 and 1007). Cancer Med. 2016;5(4):617-22. doi:10.1002/cam4.622.

10. Emelina EI, Gendlin GE, Nikitin IG, et al. Rhythm and Conduction Disorders in Patients Receiving Ibrutinib. Clinical oncohematology. 2019; 12(2):220-30. (In Russ.).

11. Brahmer JR, Lacchetti C, Schneider J, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714-68. doi:10.1200/jop.18.00005.

12. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5(1):95. doi:10.1186/s40425-017-0300-z.

13. Heinzerling L, Ott PA, Hodi FS, et al. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. J Immunother Cancer.
2016;4:50. doi:10.1186/s40425-016-0152-y.

14. Behling J, Kaes J, Munzel T, et al. New-onset third-degree atrioventricular block because of autoimmune-induced myositis under treatment with anti-programmed cell death-1 (nivolumab) for metastatic melanoma. Melanoma Res. 2017;27(2):155-8. doi:10.1097/cmr.0000000000000314.

15. Makhmudova L.I., Akhmedova N.Sh., Ergashov B.B. Clinical manifestation of irritable bowel syndrome Art of Medicine Volume-1 International Medical Scientific Journal Issue-2 P. 24-33.

16. Abdullaeva U.K. Predicting the risk of atrophic transformation in chronic gastritis using serum pepsinogen // World journal of pharmaceutical research, Faculty of Pharmacy Medical University, Bulgaria, Vol. 8, Iss. 13, 2019, P. 219-228.

18. Abdullaeva U.K., Sobirova G.N., Karimov M.M., Aslonova I.J. The prevalence and possibilities of prevention of noncardial gastric cancer in the Bukhara region // American journal of medicine and medical sciences, 2020, 10(9), P. 679-681.

19. Sobirova G.N., Abdullaeva U.K., Nosirova M.S., Aslonova I.J. Evaluation of the gastrointestinal mucosa by the OLGA system in chronic atrophic gastritis // Journal of critical reviews, Kuala Lumpur, Malaysia, Vol. 7, Iss. 2, 2020, P. 409-413.

20. Karimov M.M., Sobirova G.N., Abdullaeva U.K., Aslonova I.Zh., Tulyaganova F.M. Possibilities of serological diagnosis of atrophic processes of the gastric mucosa // European Journal of Molecular & Clinical Medicine Vol. 7, Iss. 11, 2020, P. 2955-2960.

21. Makhmudova L.I., Shazhanova N.S., Akhmedova N.Sh., (2021). Clinical Features Of Irritable Intestinal Syndrome. The American Journal of Medical Sciences and Pharmaceutical Research, 3(04), 154-159.

22. Makhmudova L.I, Akhmedova N.Sh. Irritable bowel syndrome: a new look at the problem // Academicia. 10.5958/2249-7137.2020.00983.0. 433-38

23. Abdullayev R. B., Makhmudova L.I. Features of Chemical Elements in Various Forms of Irritable Bowel Syndrome // Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 2, 2021, Pages. 2993 – 3000