

Acute Heart Failure Due to Low Doses Adriamycin

Düşük Doz Adriamisine Bağlı Akut Kalp Yetmezliği

AYŞE AYYILDIZ^a,
DEMET ÖZER^a,
EBRU KARAKOÇ^a,
BİRGÜL YELKEN^a

^aDepartment of Anesthesiology and Reanimation, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, TURKEY

Received: 12.11.2018
Received in revised form: 31.01.2019
Accepted: 31.01.2019
Available online: 05.02.2019

Correspondence:
Ebru KARAKOÇ
Eskişehir Osmangazi University
Faculty of Medicine,
Department of Anesthesiology and Reanimation, Eskişehir,
TURKEY/TÜRKİYE
ebrukarakoc1983@gmail.com

This study was oral presented at the 23rd National Multidisciplinary Clinical Toxicology Congress, 18-20 May 2018, Eskişehir, Turkey.

ABSTRACT Chemotherapeutics especially anthracycline derivatives have serious cardiac side effects which are generally occur by cumulative doses at chronic phase. It should be noted that this effect may also occur at low doses. An 30 years old female patient with a diagnosis of osteosarcoma was medicated totally 102 mg adriamycin as neoadjuvant chemotherapy. After first session of chemotherapy application; respiratory distress, electrocardiography changes, bilateral fluid overload in chest x ray developed and patient was hospitalized with acute heart failure diagnosis to our intensive care unit. Enalapril maleate and metoprolol were added to the medication to prevent early remodeling soon after the ejection fraction increased and the cardiac enzymes were started to decrease. The patient was discharged to oncology service after successful weaning and extubation. Regular cardiac follow-up during the chemotherapy process protects the patients from side effects of this drugs.

Keywords: Adriamycin; cardiotoxicity

ÖZET Kemoterapötikler, özellikle antrasiklin türevleri, genellikle kronik fazda kümülatif dozlarla ortaya çıkan ciddi kardiyak yan etkilere sahiptir. Bu etkinin düşük dozlarda da görülebileceği akılda tutulmalıdır. Osteosarkom tanısı alan 30 yaşında kadın hasta neoadjuvan kemoterapi olarak 102 mg adriamisin ile tedavi edilmiştir. Kemoterapi uygulamasının ilk seansından sonra; solunum sıkıntısı, elektrokardiyografi değişiklikleri, akciğer grafisinde bilateral sıvı yüklenmesi gelişmiş ve hasta yoğun bakım ünitemize akut kalp yetmezliği tanısı ile yatırılmıştır. Erken remodelingin önlenmesi için tedavisine enalapril maleat ve metoprolol eklenmiş, sonrasında ejeksiyon fraksiyonu artmış ve kardiyak enzimler düşmüştür. Hasta; başarılı weaning ve ekstübasyondan sonra onkoloji servisine taburcu edilmiştir. Kemoterapi süreci boyunca düzenli kardiyak takip, hastaları bu ilaçların yan etkilerinden korur.

Anahtar Kelimeler: Adriamisin; kardiyotoksosite

Cause of increased cancer prevalence chemotherapeutic drugs started to be used frequently. They have very serious side effects and complications especially the most mortal one is cardiac toxicity. Anthracycline derivative drugs, well known one is adriamycin, are chemotherapeutics with severe and fatal cardiac side effects. They usually cause irreversible type 1 cardiotoxicity. Cardiac side effects generally occur at cumulative doses.¹ The aim of this report is to show this fatal complications can develop not only cumulative high doses, can develop at first dose during chemotherapy.

CASE REPORT

An 30 years old female patient who had been diagnosed as osteosarcoma, was planned to be treated with preoperative neoadjuvant chemotherapy as adriamycin, cisplatin and methotrexate. Echocardiography and thorax to-

mography before chemotherapy were reported completely normal.¹ The ejection fraction before chemotherapy was at 60%. The body surface area was calculated as 1.36 m², she was medicated at 1st 2nd and 3rd day with 25 mg/m²/day adriamycin and first day 100 mg/m²/day cisplatin was added. She planned to be medicated at 3rd and 4th week 8-12 g/m²/day of methotrexate. After administration 25 mg/m²/day (totally 102 mg) adriamycin for 3 day and 136 mg cisplatin, the 5th day patient applied to emergency service with worsening in the general status, respiratory distress and febrile neutropenia. She had no chest pain but cardiac enzyme levels were high (Troponin T: 0.224 ng/mL, CK MB: 0.744 mg/L). There was sinus tachycardia, ST elevation at AVR, t wave negativity at D2-D3-AVF in electrocardiography (ECG). There were findings of bilateral fluid overload in the chest X ray. Absolute neutrophil count was 0.1 10³/μL. She was admitted to ICU because of increased respiratory distress, hypotension and need positive inotropic drug. In intensive care unit (ICU) first measured the ejection fraction was at 31% (Figure 1). The patient was intubated and mechanically ventilated. Cardiac enzyme levels showed an increase in ICU (PRO-BNP: 8536 pg/mL, Trop T: 0.939 ng/mL). Enalapril maleate and metoprolol were added to medications to prevent premature remodeling of the patient with acute heart failure due to chemotherapeutic toxicity. The inotropic requirement of the patient gradually decreased and was

discontinued at the end of the third day. In one week follow up in ICU cardiac enzyme levels decreased (PRO-BNP: 5043 pg/mL, Troponin T: 0.206 ng/mL) and second echocardiography in ICU before discharge the ejection fraction was measured as 48% (Figure 2). The patient was discharged to oncology service after successful weaning and extubation. After the patient gave informed consent this case report was designed.

DISCUSSION

Cardiac insufficiency due to the increased number of cancer patients receiving chemotherapy has become increasingly common. Incidence of heart failure due to chemotherapy is 1-5%, symptom-free left ventricular dysfunction rate is 5-20%. Heart failure may occur at acute phase in rare cases like our patient or it may occur subacute and chronic phase.¹ Anthracycline derivative drugs like adriamycin cause permanent myocardial damage (type 1 cardiotoxicity) started with the first dose and cumulative effect at repeated doses. Chemotherapeutic activity of anthracycline derivative drugs is based on inhibition of topoisomerase II enzyme. They may cause cell damage by free oxygen radicals formed with combination of ferrum. Myocytes, which are sensitive to cell death caused by free oxygen radicals, are the most affected cell type. Indications of anthracycline derivative drugs as chemotherapeutics are restricted due to cardiotoxic side effects.^{2,3} Type 2 cardiotoxicity usually does

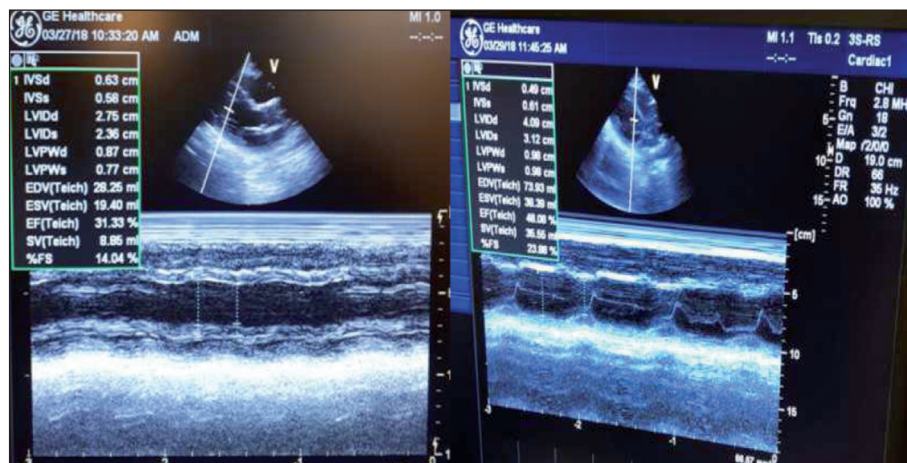


FIGURE 1: a) First echocardiography after ICU hospitalization (EF 31%) left one b) Second echocardiography in ICU after medical therapy (EF 48%) right one.

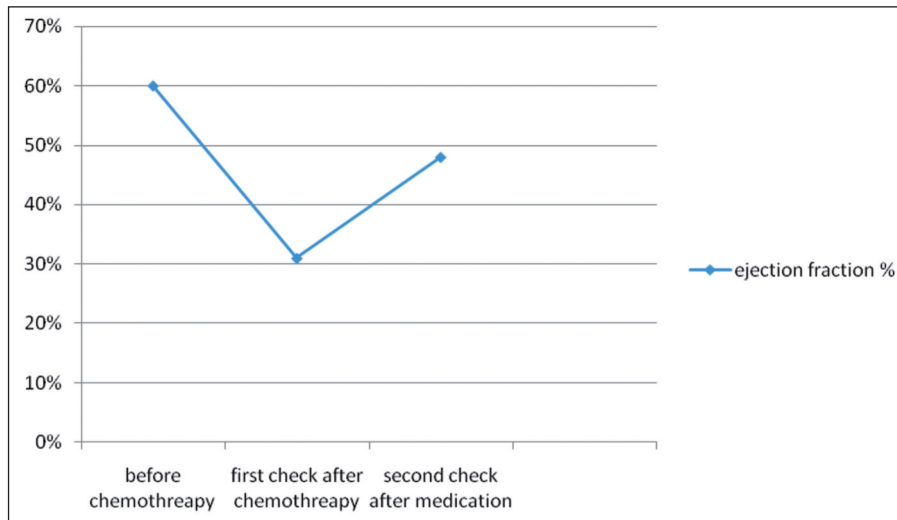


FIGURE 2: Ejection fraction values.

not lead to permanent damage and it is reversible in which loss of cellular function is at the forefront. Trastuzumab is the prototype of this group.^{4,5} It has been reported that prevention and attenuation of antracycline induced heart failure is possible in some therapeutic protocols. Limitation of antracycline doses in combination therapy procedures like R-CHOP may decrease antracycline induced heart failure. Early recognition and treatment of side effects like nausea, vomiting, diarrhea also may prevent progressive cardiotoxicity.⁵

Combination with radiotherapy, the use of overdose adriamycin (>550 mg/m²), hypertension, female sex and early age are known as risk factors of developing type 1 cardiac damage.^{5,6} In our case, only early age and female sex were present as risk factors.

It should be kept in mind that sinus tachycardia, supraventricular tachycardia, premature beats, isolated cardiac enzyme elevation and heart failure may occur in cumulative doses of adriamycin (>550 mg/m²). This side effects are usually not expected at doses below 400 mg/m² at which the risk of cardiotoxicity was 0.14%.⁶ Also in our case the patient received only 102 mg adriamycin that is grouped at the 0.14 percentage.

ACE inhibitors and beta (β) blockers protect the patient from remodeling in the early period, extend the life span. Positive clinical response is seen if these drugs are added to medication early.^{7,8}

In this case ACE inhibitors and β blockers were medicated early and we observed an improvement of ejection fraction after therapy.

Increased troponin levels during chemotherapy are considered as biomarkers in recent years in terms of cardiac toxicity occurrence. Permanent high troponin levels are associated with poor survival. In our case permanent high troponin levels were measured (the last Trop T: 0.206 ng/mL). It is emphasized that the level of the troponin should be measured regularly during treatment with cardiotoxic chemotherapeutics.⁷

A detailed cardiac evaluation is absolutely necessary before chemotherapy starts. Regular follow-up throughout the chemotherapy will protect patients from side effects of drugs and provides early diagnosis and treatment. It should be kept in mind that in some patients it may rarely occur in the first or low doses like our case.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or

members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Ayşe Ayyıldız, Birgül Yelken; **Design:** Ayşe Ayyıldız, Demet Özer; **Control/Supervision:** Ayşe Ayyıldız,

Ebru Karakoç; **Data Collection and/or Processing:** Ayşe Ayyıldız, Demet Özer; **Analysis and/or Interpretation:** Ayşe Ayyıldız, Ebru Karakoç, Birgül Yelken; **Literature Review:** Ayşe Ayyıldız, Ebru Karakoç, Birgül Yelken; **Writing the Article:** Ayşe Ayyıldız; **Critical Review:** Ayşe Ayyıldız, Ebru Karakoç; **References and Findings:** Ayşe Ayyıldız, Ebru Karakoç; **Materials:** Ayşe Ayyıldız, Demet Özer.

REFERENCES

- Shakir DK, Rasul KI. Chemotherapy induced cardiomyopathy: pathogenesis, monitoring and management. J Clin Med Res. 2009;1(1):8-12. [Crossref]
- Watts RG. Severe and fatal anthracycline cardiotoxicity at cumulative doses below 400 mg/m²: evidence for enhanced toxicity with multiagent chemotherapy. Am J Hematol. 1991;36(3):217-8. [Crossref] [PubMed]
- Quryshi N, Norwood Toro LE, Ait-Aissa K, Kong A, Beyer AM. Chemotherapeutic-induced cardiovascular dysfunction: physiological effects, early detection-the role of telomerase to counteract mitochondrial defects and oxidative stress. Int J Mol Sci. 2018;19(3):797. [Crossref] [PubMed] [PMC]
- Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol. 2005;23(13):2900-2. [Crossref] [PubMed]
- Sharalaya Z, Collier P. Prevention of cardiotoxicities with traditional and novel chemotherapeutic agents. Curr Heart Fail Rep. 2018 Jun 25. Doi: 10.1007/s11897-018-0400-1. [Epub ahead of print].
- Yayla Ç, Çay S. Kemoterapi sırasında kalp yetersizliği. Türk Kardiyoloji Seminerleri Dergisi 2014;176-85.
- Cardinale D, Colombo A, Sandri MT, Laman-tia G, Colombo N, Civelli M, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation. 2006;114(23):2474-81. [Crossref] [PubMed]
- Georgakopoulos P, Roussou P, Matsakas E, Karavidas A, Anagnostopoulos N, Marinakis T, et al. Cardioprotective effect of metoprolol and enalapril in doxorubicin-treated lymphoma patients: a prospective, parallel-group, randomized, controlled study with 36-month follow-up. Am J Hematol. 2010;85(11):894-6. [Crossref] [PubMed]