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Cardiotoxicity of antineoplasic agents: onset, risk factors and clinical manifestation

Maria L. Rădulescu, Caius L. Duncea, Dan Rădulescu, Valentin Militaru, and Andreea Pârv

5th Medical Clinic, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Cluj, România. Corresponding author: M. L. Rădulescu, lili_m_radulescu@yahoo.com.

Abstract. The continuously growing incidence of the neoplasic disease, estimated to be in 2020 the main cause of death in developed countries, has imposed an increasing research to discover new classes of antineoplasic agents, which alone or in combination with classical chemotherapy agents, may turn cancer into a curable disease for the most of the patients. All these drugs affect the heart in relation to the presence of risk factors: physiological (age, sex, race), general (malaise, pre-existing chronic diseases), pre-existing cardiovascular affections, previous mediastinal radiation therapy, association with other cardiotoxic substances, as well as in relation to factors related to medication (high daily dose, high cumulative dose, short interval between administrations, bolus injection). The mechanism that produces cardiotoxicity is incompletely elucidated, it appears to be plurifactorial, the production of oxygen free radicals being the main cause of morphological alterations. Anthracyclines cardiotoxicity is better known, with its two forms (acute/subacute and late or chronic) or even the delayed cardiotoxicity form in survivors of childhood cancers. There are also presented some cardiac damage modalities after treatment with alkylating agents, antimetabolites, taxanes, monoclonal antibodies (trastuzumab).
Key words: neoplasic disease, chemotherapy, cardiotoxicity.

Introduction. Cardiotoxicity is the most feared adverse effect of anticancer therapy, due to the fact that life expectancy obtained as a result of the anticancer treatment, may be reduced by the death rate determined by cardiac problems arising as a consequence to the treatment (Perry et al 1984; Rolles 2002; Pelengaris & Khan 2007; Jemal et al 2010).

Antineoplasic therapy includes both classic chemotherapy agents, and new "intelligent" molecules representing "the tools" of targeted molecular therapy, these classes of drugs affecting the heart, more or less (Pelengaris & Khan 2007).

Anthracyclines cardiotoxicity. The anthracyclines, broad spectrum antimetabolic antibiotics, play an important role in the treatment of leukemia, lymphoma and many solid tumors.

Due to their widespread use there is a great experience in terms of cardiac adverse effects induced by them. Identifying risk factors for developing anthracycline-induced cardiotoxicity is of vital importance as it helps the clinician to recommend different cumulative doses of chemotherapy so that its effect should be minimized.

For most tumors there is a clear dose – effect relationship. But, at the same time, the major risk factor for cardiac adverse effects is dose related and increases with the total dose of anthracyclines (Rolles 2002).

The most used anthracycline is doxorubicin. Epirubicin is considered to be less cardiotoxic, but is also less efficient.

Table 1

Indications and usual doses for the main anthracyclines

ICD	*Indications*	*Recommended daily dose*	*Total cumulative dose*
Doxorubicin	Carcinomas Lymphoma Sarcomas	60-75 mg/m^2	450 mg/m^2
Daunorubicin	Acute leukemia	40-60 mg/m^2	600 mg/m^2
Epirubicin	Carcinomas Lymphoma Sarcomas	40-100 mg/m^2	900 mg/m^2
Indarubicin	Acute leukemia	8-13 mg/m^2	225 mg/m^2

Risk factors for cardiotoxicity

- Physiological:
  1. Age: patients over 65-70 years and under 15 years
  2. Females
  3. Race: Black patients have a 25% higher rate of developing cardiovascular disease induced by anthracyclines compared with white patients (Perry 1984; Rolles 2002; Hoppe 2007).
- General:
  1. Malaise
  2. Pre-existing severe chronic diseases
- Pre-existing cardiovascular diseases
  1. Heart failure: NYHA classes I-III require dosage reduction and class NYHA IV represents an absolute contraindication to treatment with anthracyclines.
  2. Coronary disease represents an absolute contraindication to therapy when the heart pump function is severely impaired.
  3. Cardiac arrhythmias represent an absolute contraindication when they cause a major hemodynamic injury
  4. Decompensated cardiomyopathy
- Drug interactions:
  1. Previous mediastinal radiation therapy
  2. Concomitant administration of other cardiotoxic substances and chemotherapy: Bleomycin, Cyclophosphamide, Actinomicine D
- Other factors related to drug
  1. Large cumulative dose
  2. High daily dose
  3. Short interval between administrations
  4. Bolus injection

After Tokaz and Von Hoff, in patients who received a cumulative doxorubicin dose less than 550 mg/m^2 the incidence of heart failure was 0.1-0.2%, and in patients who received a cumulative doxorubicin dose more than 550 mg/m^2 (560-1155 mg/m^2) the incidence of congestive heart failure was about 30%.

It seems that the rate of epirubicin-induced cardiotoxicity increases by 40% every 100 mg/m^2 cumulative dose increase, regardless of the maximum cumulative dose considered (Basser & Green 1993; Doyle et al 2005; Appel et al 2007; Ryberg et al 2008).

Ways of cardiotoxicity manifestation. Cardiotoxicity induced by anthracyclines appears clinically in two forms: **Acute/ subacute cardiotoxicity** appears in the first 10

days of treatment, it is not correlated with the total dose of anthracycline administered and it is generally reversible. In most cases, it is represented by electrocardiographic changes and cardiac arrhythmias. Sudden deaths have been rarely reported as a consequence of anthracyclines administration. The most frequently encountered are non-specific T-wave and ST interval changes, sinus tachycardia, ventricular extrasystoles, microvoltage of QRS complex and ventricular ectopia. There can also be met atrioventricular blocks at different levels, bradycardia and ventricular tachycardia. Of these, only the QRS microvoltage may remain permanently. Note that most cancer patients may have anemia, fever and malnutrition, which in turn can cause EKG abnormalities.

Late (chronic) cardiotoxicity is mainly represented by cardiomyopathy, but there may be cases of pericarditis and myocardial infarction. Cardiomyopathy is the most severe form of anthracycline-induced cardiotoxicity leading eventually to congestive heart failure. The reported incidence of cardiotoxicity induced by anthracyclines varies greatly in the studies, due to the use of different definitions and assessment methods, different populations and different evaluation period. However, it is generally accepted that congestive heart failure is progressive and its incidence increases with the cumulative dose. Even low doses of anthracyclines may reduce cardiac left and subclinical myocardial changes). It is also widely accepted that with doxorubicin treatment cardiotoxicity incidence dramatically increases over the cumulative dose of 550 mg/m^2, but exact percentages vary from author to author: patients who received a cumulative dose under 400 mg/m^2 present a 0 incidence, 14%, a 4-18% incidence has been reported in patients with cumulative doses between 500-600 mg/m^2, over 36% at a cumulative dose more than 600 mg/m^2. Von Hoff reported an incidence of 3% at 400 mg/m^2, 7% and 18% of 700 mg/m^2 and 550 mg/m^2. Swain et al report an incidence of 5% at 400 mg/m^2, 26% at 550 mg/m^2 and 48 % at 700 mg/m^2. Congestive heart failure may manifest clinically by dyspnea, exercise intolerance, turgid jugular veins, hepatomegaly, cardiac edema, heart gallop rhythm, and cardiomegaly. Heart failure occurs in about 25-60 days after treatment, but there are also reported extremes (0-320 days) (Basser & Green 1993; Aviles 2001; Kremer et al 2002; Aviles et al 2006; Appel et al 2007; Brouwer et al 2007; Scully & Shultz 2007; Ryberg et al 2008).

Delayed cardiotoxicity has been studied mainly in patients treated for childhood cancer and who may develop possibly reversible heart failure, correlated with the cumulative anthracycline dose, in less than one year after treatment. Study results on survivors of childhood cancer (Childhood Cancer Survivor Study CCSS) show that 15-25 years after diagnosis, childhood cancer survivors have an 8.2 higher rate for cardiac death compared with the national average for the same age and same sex. Although no one can accept a safe dose of anthracyclines (both children and adults), a recent study reported no deterioration of cardiac function in patients treated with low cumulative doses of doxorubicin (100 mg/m^2) for acute lymphoblastic leukemia 20 years from diagnosis. Aviles et al report no cardiotoxicity in a group of children exposed to anthracyclines during pregnancy, and also lack of cardiotoxicity during long-term evaluation (Aviles 2001; Kremer et al 2002; Aviles et al 2006; Brouwer et al 2007; Scully & Shultz 2007; Lipshultz et al 2008).

The mechanism of induced cardiotoxicity. The mechanism by which anthracyclines cause cardiotoxicity is incompletely elucidated and appears to be multifactorial. It seems that the production of free radicals of oxygen is involved. Although reactive oxygen species are capable of producing DNA breaks in the chain of production of free radicals of anthracyclines, it has an insignificant role in producing therapeutic effects, but it represents the main factor incriminated in producing cardiotoxicity.

Anthracyclines can cause the formation of reactive oxygen species both enzymatically and by formation of stable anthracycline-iron complexes. The quinone part of anthracyclines can be reduced by cytosolic enzymes to semiquinone, which can then donate an electron to oxygen generating superoxide anions. Superoxide anion can lead

to subcellular destructions directly or by its convertion to hydrogen peroxide and reactive hydroxyl radical (Basser & Green 1993; Aviles 2001; Kremer et al 2002; Aviles et al 2006; Appel et al 2007; Scully & Shultz 2007; Ryberg et al 2008). These agents are highly toxic and react with lipids, proteins and nucleic acids causing lipid peroxidation, depletion of peptides containing sulfhydryl groups and destructions of the DNA. The reaction sequence is as follows:

1. Fe^3 + - + e-→ Fe^2 Dox + - Dox
2. Fe^2 + - + O_2 → Fe^3 + Dox - Dox + O_2-(superoxide)
3. $2O_2$ • - + 2H + + O_2 → H_2O_2 (hydrogen peroxide)
4. Fe^2 + - Fe^3 + Dox + H_2O_2 → - Dox + OH-+ OH • (hydroxyl radical)

The cardiac muscle has a smaller amount of scavenger enzymes for free radicals (catalase and glutathione-peroxidase) in comparison with other organs, making cardiac cells more susceptible to injuries caused by reactive oxygen species. Increased susceptibility of heart cells for the effects of free radicals is also determined by the intense metabolic activity of the myocardium and by the high concentration of cardiolipin, a polyunsaturated phospholipid found in the mitochondrial membrane, which presents a high affinity for anthracyclines. Anthracyclines are believed to penetrate inside the mitochondria and inhibit the respiratory chain binding it to cardiolipin or interacting with the mitochondrial DNA.

The oxidative effects of anthracyclines do not occur only in the myocardium, but tissues with high cell division rate can replace cells lost by apoptosis or necrosis, whereas myocardial cells divide very slowly or not at all, leading to insufficient replacement of the damaged cells during treatment. Functional myocytes try to compensate the massive loss by hypertrophy and thus maintain the normal heart function and structure. Remaining myocytes become fewer and fewer, and cannot compensate any more for the loss of cardiac cells, which ultimately lead to the onset of heart failure.

Cardiotoxicity of alkylating agents. Cyclophosphamide with no cardiotoxicity in standard doses, causes cardiotoxicity in high doses (Baello et al 1986; Braverman et al 1991; Gottdiener et al 1991; Ayash et al 1992; Auner et al 2002; Perez et al 2005; Mythili et al 2007; Zver et al 2008).

Its therapeutic and toxic effects are related to the need for metabolic activation by the microsomal cytochrome P450 in the liver. Cyclophosphamide-induced cardiotoxicity is dose dependent, but does not appear to be cumulative, as cardiotoxicity induced by anthracyclines. There is no evidence to support a cumulative cardiotoxicity after repeated low or moderate doses of cyclophosphamide.

The incidence of cardiotoxicity at doses over 120-150 mg/kg is of 8-20% in adults, and 5% in children. The incidence of heart failure after high doses of cyclophosphamide varies widely from author to author: less than 5% and 10-29% (Baello et al 1986; Braverman et al 1991; Zver et al 2008; Gottdiener et al 1991; Ayash et al 1992; Auner et al 2002).

Acute myocarditis and congestive heart failure install at doses over 120-150 mg/kg. Symptoms appear 1-10 days after the first dose and last 1-6 days. There seems to be no late or cumulative cardiotoxicity after the acute event. Echocardiography demonstrates an acute and reversible decrease of the left ventricular ejection fraction and a left ventricular hypertrophy.

EKG changes may occur in the absence of clinical manifestations and are represented by non-specific changes in the ST segment, the T wave inversion and the microvoltage of the QRS complex. They appear 1-3 days after cyclophosphamide administration and are reversible after treatment.

So far, there could not be established clear risk factors, which may identify patients at risk for developing cardiotoxicity after treatment with cyclophosphamide, except for high doses of cyclophosphamide (over 120-150 mg/kg). Patients who received treatment with other cardiotoxic drugs, especially anthracyclines, are more likely to develop cardiotoxicity, probably due to subclinical cardiotoxicity induced by these drugs. Prior or concomitant radiation therapy also increases the risk of cardiotoxicity. However, Auner et al showed in a study published in 2002 the lack of cardiotoxicity attributed to a

high-dose cyclophosphamide regimen and radiation therapy in patients without pre-existing heart disease and who have not previously received anthracyclines (Braverman et al 1991; Gottdiener et al 1991; Ayash et al 1992; Auner et al 2002).

In fatal cases histological examination showed extended hemorrhagic cardiac necrosis with intercapillar microthrombi and vascular endothelial destructions. The mechanism to produce these lesions is not clear. It is possible that after endothelial destructions, the toxic metabolite transweld, leading to myocytes destructions, interstitial hemorrhage, edema and appearance of microthrombi responsible for the occurrence of myocardial ischemia.

The extravasation of sero-hemorrhagic fluid in the pericardium was also highlighted, and can clinically manifest by chest pain and signs of pericarditis ((Baello et al 1986; Braverman et al 1991; Gottdiener et al 1991; Ayash et al 1992; Auner et al 2002; Perez et al 2005; Zver et al 2008).

The iphosphamide can cause some problems similar to cyclophosphamide administration: acute heart failure at 1-3 weeks after beginning treatment reversible upon discontinuation. Incidence of heart failure is correlated with the dose of administered iphosphamide: 10% of patients treated with a dose of more than 12.5 g/m2, 30% in patients receiving more than 16 g/m2, and 60% at a dose of 18 g/m2. Cardiac enzymes do not present pathological changes, and the EKG shows no ischemic changes (Baello et al 1986; Braverman et al 1991; Gottdiener et al 1991; Ayash et al 1992; Auner et al 2002; Perez et al 2005; Mythili et al 2007; Zver et al 2008).

In addition to acute heart failure, iphosphamide can cause rhythm disorders such as sinus tachycardia or supraventricular tachycardia.

It is important that iphosphamide is nephrotoxic. Decreased glomerular filtration occurs before the onset of acute heart failure, which potentiates the cardiotoxic effect by reducing the clearance of cardiotoxic metabolites.

Melphalan is an alkylating agent whose possibility of inducing cardiotoxicity is unclear. Genetic polymorphism seems to play an important role in its metabolization.

Cisplatin rarely induces supraventricular arrhythmias, nonspecific changes of the ST segment and of the T wave, a bundle branch block and heart failure. These cardiac events do not appear to be dose-related and may occur at any time since the first hours of treatment and up to 18 months after treatment. There can be seen a slight increase of cardiac enzymes, especially of the MB isoenzyme. Echocardiography may be normal or may reveal a slight decrease in the left ventricular ejection fraction and myocardial hypokinesis or akinesis.

Busulphan, alkilant agent with limited antitumour activity, rarely produces cardiotoxicity. In high doses and in combination with ciclophosphamide, busulphan is used in treatments previous to spinal cord transplant and solid tumors in children.

The main complication of busulphan therapy is represented by the pulmonary fibrosis.

In terms of cardiotoxicity only 2 cases of endocardial fibrosis and one cardiac tamponade have been described. Endocardial fibrosis was observed in 3-9 years after treatment and at a total dose of 7200 mg.

Cardiotoxicity of antimetabolites. 5-Ffluorouracil is a pyrimidine antimetabolite, whose mechanism of action depends on the mode of administration: bolus or continuous infusion. It is a well-tolerated chemotherapy and one of the most important palliative chemotherapy.

It is assumed that 5-Fluorouracil produces cardiotoxicity by interfering with the energetic metabolism of myocardial cells, thereby increasing the energetic needs of the myocardium. Another mechanism of producing cardiotoxicity involves the action of endothelin, which can cause vasoconstriction and ischemia. This theory is based on observation of an increase of the endothelin concentration in the plasma of patients treated with 5 Fluorouracil and who showed symptoms of cardiotoxicity.

The clinical panel induced by 5-Fluorouracil is acute cardiac ischemia, with angina, hypotension and even myocardial infarction. Electrocardiographically, typical changes of angina or myocardial infarction are found.

On rare occasion the following can be encountered: atrial fibrillation, QRS complex extension, ventricular extrasystoles, ventricular sustained and not sustained tachycardia and ventricular fibrillation.

Cardiotoxicity usually appears after the first or second dose and it is more common after high-dose continuous infusion (over 800 mg/m^2/day) vs. bolus. Symptoms usually appear within 72 hours of starting treatment and most of them disappear two days after treatment, but approximately 90% reappear on re-treatment. There is no late sequel of cardiotoxicity, only if the patient suffered a myocardial infarction after treatment with 5-Fluorouracil. Induced symptoms are commonly caused by coronary spasm.

The major risk factor for cardiotoxicity induced by 5-Fluorouracil is represented by the pre-existing ischemic heart disease. Previous mediastinal radiation therapy should also be considered, as it may produce alterations in the coronary arteries. Most oncologists will not prescribe 5-Fluorouracil to patients who present angina pains, but unfortunately prevalence of silent ischemic disease is high, making it difficult or even impossible to select patients who can safely receive this medication.

Cardiotoxicity induced by taxanes. The main representatives of this class, paclitaxel and docetaxel may be administered in combination with anthracyclines or alone.

Due to the importance of the antitumor activity of paclitaxel, and especially due to treatment response in patients previously not responsive to the treatment with the anthracyclines received, several studies were conducted to evaluate the doxorubicin-paclitaxel combination. Interaction between these two drugs causes a plasma and tissue increase of doxorubicin and its metabolite, doxorubicinol, the more, the shorter the interval between administrations of the two drugs is and the shorter the duration of infusion of paclitaxel is. However Gianni et al concluded that up to a cumulative doxorubicin dose of 380 mg/m^2 incidence of congestive heart failure is less than 5% regardless of the interval between administration of both drugs (Ward et al 2007; Gianni et al 2009).

Both docetaxel and paclitaxel exert their action by stabilizing microtubules and so cause an accumulation of microtubules. Increasing the density of microtubules causes a contractile dysfunction in cardiac hypertrophy (Gianni et al 2009).

Trastuzumab – induced cardiotoxicity. Trastuzumab is a monoclonal antibody that selectively inhibits cancer cell growth and proliferation in breast cancer, which expresses the HER2 protein. It is used to treat metastatic breast cancer.

Trastuzumab-induced cardiotoxicity occurs both when administered alone and in combination with other chemotherapy, especially in combination with anthracyclines (Perez et al 2005; Keefe et al 2009).

The cardiotoxicity incidence is estimated at 4% in monotherapy and 27% when tratuzumab is given in combination with anthracyclines and cyclophosphamide. Severe complications such as death or permanent disability are rare, most reported cardiac effects are mild or moderate, non-specific and respond to medical treatment.

Few detailed prospective studies have been carried out to evaluate cardiotoxicity. Most cardiac events seem to be asymptomatic losses of the left ventricular ejection fraction (LVEF), whose importance is not yet clear. When signs and symptoms are reported, they are mild to moderate and are represented by: tachycardia, palpitations, dyspnea and occasional chest pain that may progress to heart failure.

Although not yet demonstrated, tachycardia may be an early and sensitive sign in detecting cardiotoxicity induced by trastuzumab.

There is no evidence that trastuzumab-induced cardiotoxicity is dose-dependent. The incidence of severe toxicity is low with trastuzumab and is at least partially reversible in most patients. After standard treatment of heart failure or after treatment break with trastuzumab there is usually an improvement in the ejection fraction and of the symptoms and signs, although a small number of patients may still present a severe heart failure.

Risk factors for the development of trastuzumab cardiotoxicity are represented by: treatment in combination with other chemotherapy (the highest risk is represented by the association with anthracyclines), aged over 60, a previous cumulative dose of anthracycline over or of 400mg/mp, previous mediastinal irradiation, pre-existing heart disease (Tripathy et al 2004; Perez et al 2005; Keefe et al 2009).

Pathogenesis of cardiotoxicity induced by trastuzumab is still under study. HER2 plays an important role in cardiogenesis and in cardiac hypertrophy and recent studies have proved the existence of HER2 in the human cardiac tissue, which allows a directly mediated cardiotoxic effect by the HER2 cardiac receptor (Crone et al 2002; Ozcelik et al 2002; Grazette et al 2004; Tripathy et al 2004).

References

Appel J. M., Nielsen D., Zerahn B. O., Jensen B. V., Skagen K., 2007 Anthracycline-induced chronic cardiotoxicity and heart failure. Anca Oncologie **46**(5):576-580.

Auner H., Tinchon C., Brezinschek R., Eibl M., Sormann S., Maizen., et al, 2002 Monitoring of cardiac function by serum cardiac troponin T levels, ventricular repolarization indices, and echocardiography after conditioning with fractionated total body irradiation and high-dose cyclophosphamide. Eur J Haematol **69**:1-6.

Aviles A., Neri N., Nambo M., 2008 Long-term evaluation of cardiac function in children who received antracyclines during pregnancy. Annal Oncol **17**(2):286-288.

Aviles A., 2001 Hematological malignancies and pregnancy. A final report of 84 children who recived chemoterapy in to utero. Clin Lymph **2**:173-177.

Ayash L., Wright J., Tretyakov O., Gonin R., Elias A., Wheeler C., et al, 1992 Cyclophosphamide pharmacokinetics: correlation with cardiac toxicity and tumor response, J Clin Oncol **10**:995-1000.

Baello E., Ensberg M., Ferguson D., 1986 Effect of high-dose cyclophosphamide and total body irradiation on left ventricular function in adult patients with leukemia undergoing allogenic bone marrow transplantation. Cancer Treat Rep **70**:1187-1193.

Basser R. L., Green M., 1993 Strategies for the prevention of anthrayclines cardiotoxicity. Cancer Treat Rev **13**:57-77.

Braverman A., Antin J., Plappert M., 1991 Cyclophosphamide cardiotoxicity in bone marrow transplantation: prospective evaluation of new dosing regimens. J Clin Oncol **9**:1215-1223.

Brouwer C., Gietema J., Van der Berg M., Bink-Boelkens M., Elzenga N., Haaksma J., et al, 2007 Low-dose anthracyclines in childhood Acute Lymphoblastic Leukemia (ALL): no cardiac deterioration more than 20 years post-treatment. J Clin Surviv **1**:255-260.

Crone S. A., Zhao Y. Y., Fan L., et al, 2002 Erb B2 is essential in the prevention of dilated cardiomyopathy. Nat Med **8**:459-465.

Doyle J., Neugut A., Jacobson J., Grann V., Hershman D., 2005 Chemotherapy and Cardiotoxicity in Older Breast Cancer Patients: A Population-Based Study. J Clin Oncol **23**(34):8597-8605.

Gianni L., Dombernowsky P., Sledge G., Martin M., Amadori D., Arbuck S., et al, 2001 Cardiac function following combination therapy paclitaxel and doxorubicin: An analysis of 657 women with advanced breast cancer. Ann Oncol **12**:1067-1073.

Grazette L. P., Boecker W., Matsui T., et al, 2004 Inhibition of Erb B-2causes mitochondrial dysfunction in cardiomyocytes: implications for herceptin-induced cardiomyopathy. J Am Coll Cardiol **44**:2231-2238.

Gottdiener J., Appelbaum F., Ferrans V., 1991 Cardiotoxicity associated with high-dose cyclophosphamide terapy. Arch Intern Med **141**:758-763.

Hoppe U. C., 2007 Herzkrankungen bei Tumoren und Tumortherapie. Der Internist **48**(3):268-275.

Keefe D., 2002 Trastuzumab-associated Cardiotoxicity. Cancer **95**:1592-600.

Kremer L., Van der Offringa H., Van Dalen E., Voute P., 2002 Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systemic review. Annal Oncol **13**:819-829.
Lipshultz S., Alvarez J., Scully R., 2008 Anthracycline associated cardiotoxicity in survivors of childhood cancer. Heart **94**:525-533.
Mythili Y., Sudharsan P., Amudha G., Varalakshmi P., 2007 Effect of DL-α-lipoic on cyclophosphamide induced lysosomal changes in oxidative cardiotoxicity. Life Sci **80**(21):1993-1998.
Ozcelik C., Erdmann B., Pilz B., et al, 2002 Conditional mutation of the Erb B2(HER2) receptor in cardiomyocytes leads to dilated cardiomyopathy. Proc Natl Acad Sci USA **99**:8880-8885.
Perez E., Suman V., Davidson N., 2005 Interim cardiac safetly analysis of NCCTGN 9831 intergroup adjuvant trastuzumab Trial. Proc Am Soc Clin Oncol **23**:17.
Perry M. C., Yarbro J. W., 1984 Toxicity of chemotherapy, Grune and Stratton, Orlando.
Rolles R., 2002 The Cardiotoxicity of anticancer Drugs. Cardiology News **5**(4):14-19.
Ryberg M., Nielsen D., Nielsen G., Skovsgaard T., Andersen P. K., 2008 New Insight into Epirubicin Cardiac Toxicity: Competing Risks Analysis of 1097 Breast Cancer Patients. J Natl Cancer Inst **100**(15):1058-1067.
Scully R. E., Lipshultz S. E., 2007 Antracycline cardiotoxicity in long term survivors of childhood cancer. Cardiovasc Toxicol **7**:122-128.
Tripathy D., Seidman A., Keefe D., 2004 Effect of cardiac dysfunction on treatment outcomes in women receiving trastuzumab for HER 2-overexpressing metastatic breast cancer. Clin Breast Cancer **5**:293-298.
Ward S., Simpson E., Davis S., Hind D., Rees A., Wilkson A., 2007 Taxanes for the adjuvant treatment of early breast cancer: Sistemic review and economic evaluation. Health Technol Assess **11**(40):1-144.
Zver S., Zadnik V., Cernelc P., Kozelj M., 2008 Cardiac toxicity of high-dose cyclophosphamide and melphalan in patients with multiple myeloma treated with tandem autologous hematopoietic stem cell transplantation. Int J Hematol **88**:227-236.

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Authors:
Liliana Rădulescu, 5th Medical Clinic, "Iuliu Haţieganu" University of Medicine and Pharmacy, 11 Tăbăcarilor Street, 400139, Cluj-Napoca, România, EU.
Caius R. Duncea, 5th Medical Clinic, "Iuliu Haţieganu" University of Medicine and Pharmacy 11 Tăbăcarilor Street, 400139, Cluj-Napoca, România, EU, email: crduncea@yahoo.com.
Dan Rădulescu, 5th Medical Clinic, "Iuliu Haţieganu" University of Medicine and Pharmacy 11 Tăbăcarilor Street, 400139, Cluj-Napoca, România, EU, email: dan_rad31@yahoo.com.
Valentin Militaru, 5th Medical Clinic, "Iuliu Haţieganu" University of Medicine and Pharmacy, 11 Tăbăcarilor Street, 400139 Cluj-Napoca, România, EU, email: Valentin.Militaru@umfcluj.ro.
Andreea Pârv, 5th Medical Clinic, "Iuliu Haţieganu" University of Medicine and Pharmacy, 11 Tăbăcarilor Street, 400139 Cluj-Napoca, România, EU, email, aandreea20023@yahoo.com
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