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Cardiac Complications of Cancer Treatment

Beata Mlot and Piotr Rzepecki
Military Institute of Medicine,
Poland

1. Introduction

Nowadays improvement in overall survival in patients suffered from cancer is observed. It is caused by using more effective treatments. The often observed side effect of anti-cancer therapy is cardiotoxicity. The decision about further treatment in cancer patients can be affected by the risk of development of this complication.

This chapter presents examples of proven cardiac toxicity associated with oncology treatment. It describes cytotoxic drugs used in chemotherapy, new anticancer agents from the group of molecular targeted therapy, radiotherapy and supportive treatment in oncology.

Drug-induced cardiomyopathy, which is a consequence of oncological treatment may be asymptomatic or present with acute or chronic heart failure, myocardial infarction, arrhythmia or sudden cardiac death. [1]

Drug-induced toxicity can be divided depending on the time of onset:

- acute: namely, that appeared in the course of cancer therapy,
- chronic: that is to say, that occurred within 12 months of completion of oncological treatment and
- chronic delayed: that is appearing 5 years after the end of treatment. [1]

2. Cytostatics with confirmed myocardial toxicity: Anthracycline antibiotics, nitrogen mustard-derivatives (cyclophosphamide and ifosfamide), 5-fluorouracil and mitomycin C. [1,2]

2.1 Anthracycline antibiotics

Anthracycline antibiotics are compounds isolated from fungi Streptomyces percetus and Streptomyces caesius.

2.1.1 The mechanism of anticancer action of anthracyclines

- incorporation to the structure of DNA, leading directly to inhibit transcription, protein production and replication problems,
- formation of additional abnormal bonds between nitrogen bases of DNA strands, which causes disruption of DNA and RNA synthesis and impaired DNA repair mechanisms,

- interference in the process of separating the strands of DNA and helicase activity, inhibition of key enzymes in the synthesis of DNA topoisomerase I and II,
- formation of free radicals that damage DNA, causing lipid peroxidation and accumulation of proapoptotic ceramide,
- induction of apoptosis via activation of p53. [3,4,5]

2.1.2 Clinical application of anthracyclines

Due to antitumor activity of anthracycline antibiotics they are incorporated into many therapeutic regimens in both solid tumors and hematological cancers. For example, doxorubicin is used to treat breast cancer, lymphoma, Ewing sarcoma, small cell lung cancer and soft tissue sarcomas. Daunorubicin is used primarily to treat acute myeloid and lymphoblastic leukemias. [6]

The cardiotoxicity of anthracycline antibiotics has been already documented in the seventies and affects all currently used anthracyclines [2]:

- doxorubicin,
- daunorubicin,
- epirubicin,
- esorubicin,
- aklarubicin,
- idarubicin
- and mitoxantrone, derivative-anthracycline.

The newer generation of antibiotics are derivatives of liposomal anthracycline doxorubicin, which are characterized by lower cardiotoxicity compared to their predecessors. [1,2]

2.1.3 Risk factors for cardiotoxicity after treatment with anthracyclines

Toxicity of anthracycline antibiotics depends on the dose. Most published reports showed that, the possibility of permanent myocardial damage is significantly increased beyond the cumulative dose of anthracyclines.

The cumulative doses significantly increasing the risk of permanent damage of heart muscule are as follow:

- doksorubicin-550mg/m2 (450 mg/m2 when radiotherapy was used or when

other risk factors of cardiotoxicity are present),

- daunorubicin-600mg/m2,
- epirubicin-1000 mg/m2,
- esorubicin-1900 mg/m2,
- aklarubicin-2000-3000 mg/m2,
- mitoxantrone-160 mg/m2. [2]

Other risk factors of cardiotoxicity associated with anthracycline antibiotics treatment include:

- individual susceptibility of the patient,

- genetic polymorphism associated with drug transport and metabolism of free radicals,
- age (over 65 years and under 4 years),
- black race,
- Down syndrome,
- prior mediastinal irradiation of ionizing radiation dose > 20Gy,
- previous cytotoxic therapy with potentially cardiotoxic drugs,
- pre-existing heart disease (valvular, ischemic origin, etc.),
- hypertension,
- diabetes,
- liver disease, [1,2]
- higher risk for chronic heart failure is observed in women,
- late coronary events are more common in men. [7]

2.1.4 Mechanism of cardiotoxicity action of anthracyclines

Mechanisms of anthracyclines cardiotoxicity with the pathogenesis of cardiomyopathy and heart failure are not fully explained.

One hypothesis assumes that the cardiotoxic effect of anthracyclines is a consequence of damage of mitochondria by these drugs. They bind to cardiolipin forming part of the inner mitochondrial membrane. This results in unbalanced electron transport in the respiratory chain, leading to depletion of ATP and phosphocreatine stores resulting in a decrease in myocardial contractility. Doxorubicin-cardiolipin complex also causes the formation of free hydroxyl radicals and hydrogen peroxide, which contributes to further damage to cell membranes and DNA. [2] The biopsy of the myocardium after therapy with anthracylines revealed myocyte vacualization, reduce amount of myofibrils, an increased number of lysosomes and mitochondria swelling. [8] Billigham scale is used in order to evaluate the histological severity. [9]

At present the most intensive examination of factors involved in the pathogenesis of anthracycline cardiomyopathy is cardiomyocyte apoptosis. Anthracyclines induce myocyte death through changes in protein expression of Bax (a protein with Bcl-2 family, cytochrome c release through mitochondrial pore opening) and Bcl-Xl (a protein with Bcl-2 family block cytochrome c release). [10,11]

The role of iron ions is significant as well. Iron is necessary for the conversion of O2-and H2O2 into the highly reactive hydroxyl radical (OH), and other toxic compounds. They can cause death of cardiomyocytes. It is also believed that the anthracycline antibiotics disturb cellular iron homeostasis in cardiomyocytes. It is plausible that change in the dynamics of release and storage of iron ions in the intracellular resources contribute to the death of heart muscle cells. In addition, it is believed that anthracyclines reduce iron release from ferritin, thus affect important metabolic processes dependent on iron. Iron is essential for DNA synthesis and cytochromes. However, accumulation of iron in ferritin is a protective mechanism against apoptosis by slowing the reaction of free radicals. [12,13]

Another possible mechanism of anthracyclines cardiotoxicity is the influence of anthracyclines on the calcium homeostasis. Before leading to apoptosis, oxidative stress can induce mitochondrial permeability transition with alterations in mitochondrial calcium

transport. Changes in calcium transport can lead to tissue injury, cell killing and impaired cardiac contraction. In vitro doxorubicin treatment caused an irreversible decrease in mitochondrial calcium loading capacity. Moreover, anthracyclines can stimulate the release of calcium from isolated cardiac and skeletal muscle sarcoplasmic reticulum vesicles. This is strengthened by the observation of Rossi *et al*. who found a protective effect of the calcium blocking agent verapamil on doxorubicin induced cardiotoxicity in rats. This effect would be due to the calcium blocking capacities of verapamil inhibiting the intracellular calcium overload and antagonizing the effect of doxorubicin on mitochondria. However, others have demonstrated an increase in cardiotoxicity when doxorubicin was given in combination with verapamil. Different mechanisms for this effect are postulated. One is based on the capacity of verapamil to inhibit the function of P-glycoprotein and increase intracellular cytotoxic drug concentrations. This may be useful in overcoming resistance to chemotherapeutic drugs in cancer cells, but it could also lead to toxic effects in normal structures such as cardiac cells. Some studies showed in vitro increased doxorubicin accumulation in rat cardiomyocytes when incubated with a combination of verapamil and doxorubicin. Akimoto *et al* did not show an increased cellular anthracycline uptake but they found additive cardiotoxicity by verapamil due to its selective inhibition of cardiac actin gene expression, a similar effect which was demonstrated before with doxorubicin alone. The exact role of the changing capacities of doxorubicin on calcium regulation and its implications for cardiotoxicity remains to be elucidated. [2]

Recently, clinical trials evaluated the effect of anthracyclines on dysfunction of cardiac stem cells. These are undifferentiated cells, who renews themselves and differentiates into cardiac muscle cells and coronary vessels both in vitro and in vivo. Cardiac stem cells resulting in the surface receptor c-kit have been identified in the adult mammalian heart muscle. There is the evidence that the loss of cardiac stem cells with impaired production of daughter cells may be responsible for the development of anthracycline cardiomyopathy. Moreover it has been found that stem cells show efficacy in the treatment of experimentally induced heart failure. [14,15,16]

Other potential etiologies of development of anthracycline cardiomyopathy, reported in the literature are:

- effect of anthracyclines on the enzymatic antioxidant system cells, via reducition of the activity of glutathione peroxidase (GS-PX1) and the amount of copper-zinc superoxide dismutase (CuZnSOD) in cardiomyocytes,
- membrane lipid peroxidation,
- disruption of titin* (protein associated with myosin, and which is incorporated into the structure of sarcomeric),

* Titin, also known as connectin, is a protein that in humans is encoded by the TTN gene. Titin is a giant protein that functions as a molecular spring which is responsible for the passive elasticity of muscle. It is composed of 244 individually folded protein domains connected by unstructured peptide sequences. These domains unfold when the protein is stretched and refold when the tension is removed. Titin is important in the contraction of striated muscle tissues. It connects the Z line to the M line in the sarcomere. The protein contributes to force transmission at the Z line and resting tension in the I band region. It limits the range of motion of the sarcomere in tension, thus contributing to the passive stiffness of muscle.

- abnormal calcium homeostasis and cardiac contractility, reduction in expression of contractile proteins and proteins regulating intracellular calcium movement,
- inactivation of mitochondrial creatine kinase and abnormal structure of dystrophin. [17,18,19]

Acute cardiotoxicity associated with anthracyclines may occur after either first or initial few infusions of drug. It is not dose depend and presents as sinus tachycardia. It may result in myocarditis, with or without pericarditis.

The ECG changes include:

- voltage decrease.
- widening of QRS complexes.
- small R wave progression [anterior wall of heart].
- nonspecific T wave changes.

Acute cardiotoxicity associated with anthracyclines despite its the transient nature can cause life-threatening complications such as myocardial infarction, pulmonary edema, hypotension and serious arrhythmias. [20]

Chronic anthracycline cardiotoxicity occurs during the first year after treatment [10% of patients treated with anthracyclines]. It is dose-dependent. Most commonly it is manifested as exacerbation of heart failure, decrease in ejection fraction, cardiac arrhythmias, and development of dilated cardiomyopathy. A history of treatment with anthracyclines may be associated with long-term risk of cardiac complications in both children and adults. [20]

Mitoxantrone is a derivative of anthracycline-like structure similar to doxorubicin and contributes to the occurrence of left ventricular dysfunction. It has been used in the induction of remission in acute myeloid leukemia, in breast cancer and ovarian cancer resistant to chemotherapy as well as prostate cancer resistant to hormonotherapy. In the assessment of 80 patients treated with mitoxantrone, clinical congestive heart failure (CHF) was diagnosed in 1.5% of them. The risk of cardiac complications increases after the total dose of 160 mg/m2. Reduction of left ventricular EF [LVEF] was observed in patients with prior history of diseases of the cardiovascular system and with previous exposure to anthracyclines. [21]

Mechanism of cardiotoxicity action of anthracyclines is shown in Table nr 1.

2.2 Cardiotoxicity of taxanes

Cardiac complications may be caused by another group of cytostatic drugs used in oncology- the taxanes.

2.2.1 Mechanism of antitumor action of taxanes

The mechanism of antitumor action of this relatively new group of cytostatics are:

- Stabilization of microtubules, causing cell cycle blockage at the stage of mitosis.
- In addition, docetaxel can induce apoptosis by blocking the antiapoptopic action of BCL-2 gene, and by influencing the activation of the p53 gene.

At the level of myocytes	• apoptosis of cardiomyocytes as a result of changes in protein expression of Bcl-2, • mitochondrial damage, • decreasing the activity of glutathione peroxidase (GSH-PX1) and the amount of copper-zinc superoxide dismutase (CuZnSOD), • abnormal cellular iron homeostasis in cardiomyocytes, • direct DNA damage of cardiomyocytes, membrane lipid peroxidation, disruption of titin, disturbances of calcium homeostasis and cardiac contractility, reduced expression of contractile proteins and proteins regulating intracellular calcium movement, inactivation of mitochondrial creatine kinase and abnormal structure of dystrophin.
At the level of cardiac stem cells (SKM)	• induction of apoptosis and inhibition of proliferation of SKM through increased oxidative DNA damage and telomere shortening.

Table 1. Mechanisms of cardiotoxicity action of anthracyclines

2.2.2 Clinical application of taxanes

Taxanes are used primarily in chemotherapy of solid tumors, including lung cancer, hormone-refractory prostate cancer, bladder cancer, stomach cancer, breast cancer or ovarian cancer. [22]

2.2.3 Risk factors for cardiotoxicity after treatment with taxanes

Cardiac risk factors included were age, hypertension, diabetes and prior radiotherapy to the chest wall. [2,22,23]

Docetaxel shows no increase in cardiac toxicity when combined with doxorubicin. This is in line with the observation that a pharmacokinetic interaction with doxorubicin as described for paclitaxel has not been observed. [2,22]

2.2.4 Mechanism of cardiotoxicity of taxanes

During administration of paclitaxel, whether or not combined with cisplatin, various cardiac disturbances are reported like brady- and tachyarrhythmias, atrioventricular and bundle branch blocks and cardiac ischemia. Hypotension is also reported, probably as a result of a hypersensitivity reaction. When evaluating three phase I and one phase II studies performed at the John Hopkins Institute it appeared that 5% (n = 7) of the patients showed overt cardiac disturbances as ventricular tachycardia and atrioventricular conduction abnormalities. Asymptomatic bradycardia occurred in 29% of patients receiving maximal tolerable doses (110-250 mg/m^2) of paclitaxel in the phase II study. These disturbances did not lead to clinical symptoms. The abnormalities usually started several hours following the initiation of paclitaxel therapy and resolved after discontinuation. This evident time relationship and the fact that most patients had no cardiac risk factors supports the assumption of causality between paclitaxel and the observed cardiac rhythm disturbances. [2,22,23]

Another concern with the use of taxoids has been the development of congestive heart failure in patients treated with a combination of doxorubicin and taxoids. The cardiotoxicity

associated with taxoids seems to be mild in most cases. However, in clinical trials patients with prior history of cardiac disturbances were often excluded. Therefore, the rate of cardiotoxicity in this group of patients is difficult to estimate. Study in patients with major cardiac risk factors revealed that paclitaxel could be safely administered as single therapy or in combination with a platinum agent such as cisplatin or carboplatin. Cardiac risk factors included unstable angina, severe coronary artery disease, congestive heart failure and atrial fibrillation. [2,22,23]

Paclitaxel is formulated in a cremophor EL vehicle to enhance the drug solubility and it is suggested that the vehicle and not the cytotoxic drug itself is responsible for the cardiac disturbances. However, the cardiac rhythm disturbances are not reported with use of other drugs containing cremophor EL such as cyclosporin. The possible mechanism by which cremophor EL would cause cardiotoxicity is massive histamine release. Indeed, stimulation of histamine receptors in cardiac tissue in animal studies has resulted in conduction disturbances and arrhythmias. An alternative explanation for paclitaxel induced cardiotoxicity could be the induction of cardiac muscle damage by affecting subcellular organelles. [2]

Enhanced cardiac toxicity has been found in combined therapy of paclitaxel and doxorubicin. At doses of doxorubicin exceeding 380 mg/m^2, the toxicity increased in combination therapy compared to doxorubicin single therapy. A pharmacokinetic interaction appears to be responsible for this effect as paclitaxel has been found to decrease doxorubicin hepatic elimination and lead to increased plasma concentrations of doxorubicin. This effect depends on the interval and sequence of drug administration as well as the duration of the paclitaxel infusion. [2,22]

A similar effect has been shown for epirubicin. Baldini et al. [23] evaluate cardiac safety of two different schedules of epirubicin and paclitaxel in advanced breast cancer. Patients were enrolled into a multicenter randomized phase III trial. They received epirubicin 90 mg/m2 plus paclitaxel 200 mg/m2 (3-h infusion) on day 1 every 3 weeks for eight courses (arm A), or epirubicin 120 mg/m2 on day 1 every 3 weeks for four courses followed by four courses of paclitaxel 250 mg/m2 on day 1 every 3 weeks (arm B). Baseline median left ventricular ejection fraction was 60% in arm A and 65% in arm B; after four courses, figures were 57 and 60%, respectively. After eight courses, the median left ventricular ejection fraction in arm A declined to 50% while no further reduction was detected in arm B by adding four courses of high-dose paclitaxel. Seven episodes of congestive heart failure were observed during treatment in arm A. The risk of congestive heart failure or impairment in the cardiac function correlated only with the cumulative dose of epirubicin. No impact on cardiotoxicity can be attributed to high-dose paclitaxel. [23]

2.3 Cardiotoxicity of nitrogen mustard derivatives of cyclophosphamide [CTX] and ifosfamide [IFO]

2.3.1 Cyclophosphamide

2.3.1.1 Mechanism of antitumor action of cyclophosphamide

These drugs are alkylating agents. Their biological active metabolities are responsible for their action. Cyclophosphamide and ifosfamide are alkylating oxazaphosphorine agents that

need to be metabolized in vivo in the liver to form the active cytotoxic agent phosphoramide mustard. They contain many chloroethyl groups and therefore may create cross-binding of the DNA chain, causing damage that is difficult to repair. [22]

2.3.1.2 Clinical application of cyclophosphamide

Cyclophosphamide has a very wide range of indications:

- acute myeloid leukemia,
- acute lymphoblastic leukemia,
- chronic lymphocytic leukemia,
- Hodgkin, non-Hodgkin lymphomas,
- lung, breast, ovarian and bladder cancers,
- sarcomas,
- retinoblastoma.

2.3.1.3 Risk factors for cardiotoxicity after treatment with cyclophosphamide

Cardiotoxicity of this drug depends on its dose. Described complications of the cardiovascular system occur after administration of 120 to 200 mg/kg of cyclophosphamide. [24] Some sources indicate that cardiotoxicity of cyclophosphamide may be present in 3% of patients who received a dose of less than 1.55 g/m2/daily and in 25% who received cyclophosphamide at a daily dose greater than 1.55 g/m2/daily. [25]

2.3.1.4 Mechanism of cardiotoxicity of cyclophosphamide

Cardiac complications observed in patients treated with CTX were as follows:

- ECG abnormalities in the form of low-voltage QRS wave,
- progressive heart failure,
- myocarditis or pericarditis which sometimes lead to cardiac tamponade requiring urgent pericardiocentesis.

In 90% of patients with confirmed adverse effect of cyclophosphamide on the heart muscle, there were no clinical signs of cardiac toxicity of this drug. In these cases, ones observed mild pericarditis, and slight changes in the ECG that did not require treatment and resolved spontaneously without leaving any complications. They were ST-segment abnormalities and supraventricular arrhythmias. [25-27] The Harvard Medical School studied the cardiotoxicity of cyclophosphamide, depending on the dose in the preparatory regimen before bone marrow transplantation. Cyclophosphamide (CTX) cardiotoxicity may be a lethal complication of bone marrow transplantation. Previous echocardiographic studies have reported that left ventricular dysfunction due to CTX occurs in over 50% of patients undergoing transplantation. To evaluate the cardiotoxicity of new dosing protocols that included twice-daily rather than once-daily CTX, 44 bone marrow transplantation patients were prospectively evaluated with serial ECGs and echocardiograms. Twenty-six patients received a once-daily lower-dose protocol (mean total 87 +/- 11 mg/kg), and 18 patients received a twice-daily higher-dose (mean total 174 +/- 34 mg/kg) CTX regimen. In the higher-dose CTX group, significant reductions in summed ECG voltage (-20%) (P less than 0.01) and increases in left ventricular mass index (LVMI) (+10%) (P less than 0.05) were detected in the first week following therapy. These changes resolved by the third week following CTX and were significantly greater than the changes

noted in the lower-dose group. However, LVEF did not change significantly in either group. Five patients developed clinical cardiotoxicity (four- pericarditis; one- congestive heart failure); four of the five patients were in the higher-dose group (P = 0.14). Only a prior history of congestive heart failure or a baseline EF less than 50% was an independent correlate of clinical cardiotoxicity (P less than 0.05). Thus, dose-dependent cardiotoxicity following the use of CTX for bone marrow transplantation presents as reversible decreases in ECG voltage and increases in left ventricular mass. This likely reflects myocardial edema or hemorrhage. However, systolic dysfunction is much less common with these new twice-daily dosing regimens when compared with earlier studies of high-dose once-daily CTX.

It has been proven that the cardiotoxicity of cyclophosphamide is a result of its biologically active metabolites such as 4-hydroxy cyclophosphamide (HCY), o-carboxyetyl-nitrogen mustard (CEPM), deschloroetyl-cyclophosphamide (DCCY), 4-keto-cyclophosphamide (KetoCY) and hydroxypropyl nitrogen-mustard (HPPM). [21,29] Endothelial damage by toxic metabolites of cyclophosphamide results in extravasation of blood and damage to the vessel wall myocytes resulting in intravascular hematoma with subsequent swelling. Symptoms of congestive heart failure usually appear within two weeks after drug administration. In patients in whom it is rapid, it can lead to death within a few weeks. There is evidence that the severity of the toxicity of cyclophosphamide depends on the personal attributes associated with the intensity of metabolism of this drug. [21]

2.3.2 Ifosfamide

Ifosfamide (IFO) is a structural isomer of cyclophosphamide.

2.3.2.1 Mechanism of antitumor action of ifosfamide

Mechanism of action this drug is the same like cyklophosphamide.

2.3.2.2 Clinical application of ifosfamide

This cytostatic is used to treat lung cancer, germ cell tumors, sarcomas and lymphomas, may also lead to cardiac complications.

2.3.2.3 Risk factors for cardiotoxicity after treatment with ifosfamide

The risk of congestive heart failure depends on the dose ifosfamide and increases from 8% to 67% at doses ranging from 10 g/m2 to 18 g/m2. An additional risk factor in these cases is the development of renal failure with subsequent overload the body's fluids.

2.3.2.4 Mechanism of cardiotoxicity of ifosfamide

In 15% of patients receiving a dose of this cytostatic up to 10g /m2 may experience the following variations in the ECG:

- supraventricular tachycardia,
- changes in ST-T.

The development of congestive heart failure (from mild stagnation in the circulation to a cardiogenic shock of lesser severity) occurs 6 to 23 days after starting therapy, with improvement within 4 to 7 days after discontinuation of cytostatic and appropriate treatment. Usually, it is fully reversible. Cardiac tamponade or pericardial effusion is

extremely rare. There were reports of various types of arrhythmias after various doses of ifosfamide:

- extrasystoles supraventricular or ventricular,
- supraventricular tachycardia,
- atrial fibrillation,
- atrial flutter,
- acute ventricular arrhythmias.

In addition, there were changes in the passage from the ST-T ECG and QRS voltage reduction. In a study of patients treated with fractionated doses of ifosfamide (doses ranging from 6.5 to 10 g/m2) 15% of them developed symptoms of acute cardiac toxicity in the form of supraventricular arrhythmias and changes in ST-T. The symptoms were reversible after discontinuation of treatment. In one patient re-use of ifosfamide led to the development of arrhythmias resistant to treatment. [30-34]

The possible causes of cardiac complications associated with cyclophosphamide and ifosfamide are electrolyte imbalance. The development of severe hypokalemia was described in four patients treated with ifosfamide with mesna supply. Three patients received ifosfamide at a dose of 5g /m2, and one at a dose of 4g /m2. One patient was treated with ifosfamide + mesna only, others also received mitoxantrone plus etoposide or doxorubicin and vindesine, or methotrexate and etoposide. In none of these patients other causes of hypokaliemia were found. Hypokaliemia appeared between 2 and 12 days after application of ifosfamide with mesna. One death was observed due to cardiac arrest in a patient with a potassium level of 2.2 mEq/l. In the remaining patients, the lowest potassium levels ranged from 1.7 to 2.6 mEq/l. [35-37]

Mechanism of cardiotoxicity action of nitrogen mustard derivatives is showen in Table nr 2.

• endothelial damage by toxic metabolites for example: 4-hydroxy cyclophosphamide (HCY), o-carboxyetyl-nitrogen mustard (CEPM), deschloroetyl-cyclophosphamide (DCCY), 4-keto-cyclophosphamide (KetoCY) and hydroxypropyl-nitrogen mustard (HPPM),
• electrolyte disturbances including hypokalemia

Table 2. Mechanisms of cardiotoxicity action of cyclophosphamide and ifosfamide

2.4 Cardiotoxicity of 5-fluorouracil [5-Fu]

Another chemotherapeutic agents with potentially cardiotoxic action are 5-fluorouracil (5-Fu) and its prodrug capecitabine-(4-pentoksykarbonylo-5-deoxy-5-fluorocytydyna).

2.4.1 Mechanism of antitumor action of 5-fluorouracil and capecitabine

The mechanism of antitumor action of 5-Fu is the inhibition of DNA synthesis by the active metabolite - phosphodeoksyrybonucleotide (FdUMP). In addition, 5-Fu forms additional metabolite- (5-FUTP), which can be incorporated into RNA. Thus it blocks the processing of RNA and its function.

2.4.2 Clinical application of 5-Fu and capecitabine

They are the main cytostatics used in the treatment of epithelial cancers, especially: breast, head, neck and gastrointestinal tract. [38]

2.4.3 Risk factors for cardiotoxicity after treatment with 5-Fu and capecitabine

The incidence of 5-Fu cardiotoxicity is 7.6% with mortality ranging between 2.2% and 13%. [38] Cardiac toxicity of 5-fluorouracil is dose-dependent. A cumulative dose threshold for severe heart effects has been calculated between 1.5 and 7g. [39] The risk of cardiac ischemia appears to vary ranging from 1-68% in the patients treated with high-dose infusions of 5-fluorouracil. [40] Cardiac complications after administration of a bolus occur with a frequency of 1.6-3%, while after 4-5 days of continuous infusions at a frequency of 7.6-15%.

2.4.4 Mechanism of 5-fluorouracil cardiotoxicity

The most often cardiac symptoms are:

- chest pain,
- ST-T wale changes,
- arrhytmias (for example atria fibrylattion),
- asymptomatic bradycardia,
- hypotension,
- cardiogenic shocks,
- cardiac failure,
- acute coronary syndrome.

But most common finding is reversible ST-T wave changes. [41] Fidan et al. [42] described a 46-year-old patient with stomach cancer, in whom the administration of 5-Fu in the bolus as the adjuvant chemoradiotherapy attack of ventricular fibrillation occurred. It was accompanied by a decrease in EF to 40%. This complication is extremely rare after administration of 5-Fu in the bolus. It has been proved that the administration of the drug in the form of short-term injection is safer than continuous infusions. [42]

The literature describes several potential mechanisms of toxicity of 5-Fu on the cardiovascular system. Many authors claim that the basic mechanism is due to coronary artery spasm. Ischemia could be because of direct tonic effect on the vascular endothelium involving NO synthase, which leads to coronary vasospasm. The other mechanism of vasospasm endothelial vasoconstriction is via protein kinase C. The hypothesis that endothelin-1 (ET1) release could be involved in 5-Fu cardiotoxicity has never been substantiated. 5-Fu can also damage endothelium, causing thrombus formation and vascular endothelial release of vasoactive substances. A reduction of antioxidant defense capacities in myocardial tissues and modulation of the immune response are other potential causes of 5-Fu cardiotoxicity. The administration of 400 mg/kg/day of 5-Fu to guinea-pigs reduced the activity of the cardiac enzymes: superoxide dismutase and glutathione peroxidase. Concomitantly there was an increase in the activity of catalases and malondialdehyde concentrations. Interestingly, an increase in malondialdehyde concentrations is consistently observed in myocardial ischemia and this increase is prevented or reversed by calcium inhibitors. A proliferation of the sarcoplasmic reticulum

with vacuolizations similar to that occurring with anthracyclines was also reproted with 5-Fu. [38,43] According to Labianca et al.,[44] the global incidence of heart lesions associated with 5-Fu is higher in patients with a cardiac history in comparison to patients with no cardiac history (4.5 versus 1.1%). [44] The risk of 5-Fu cardiotoxicity was increased in 5-Fu-treated patients receiving mediastinal radiotherapy. [45] However Tsibiribi et al. [43] described cardiac complications in 16 out of 1350 patients treated with 5-Fu with a negative history of diseases of the cardiovascular system. Ten patients complained of angina pectoris. Two were asymptomatic, but had electrocardiographic changes indicative of myocardial ischemia. Three patients had clinical symptoms without EKG changes. Heart failure was observed in one patient. [43]

2.4.5 Mechanism of cardiotoxicity of capecitabine

While cardiac events associated with the use of 5-Fu are a well known side effect, capecitabine-induced cardiotoxicity has been only rarely reported. Capecitabine is an orally active prodrug of 5-Fu and breast cancer and colon cancer exhibits antitumor efficacy comparable to 5-Fu. Capecitabine is converted to the active 5-Fu by the action of a series of enzymes. One of these enzymes, thymidine phosphorylase (TP), has higher concentrations in tumor tissue than in normal tissue. This suggests that the activation occurs preferentially in tumor tissue, providing a favorable ratio for toxicity and radiosensitization. [46] In a retrospective analysis performed on studies of patients unergoing chemotherapy for metastatic breast and colon cancer, the incidence of cardiotoxicity with capecitabine was found to be comparable to that of 5-Fu. [47] Wijesinghe et al [48] reported an acute coronary syndrome in a patient with no history of cardiovascular disease who had been on capecitabine for only 2 days. [48] Kosmas et al documented myocardial infarction, electrocardiographic abnormalities, and ventricular extrasystoles in patients on capecitabine. [49] Furthermore, Goldsmith et al recently reported exercise-induced global myocardial ischemia with an ejection fraction of 36% in a patient with normal coronary arteries and resting left ventricular function who was on capecitabine for recurrent breast cancer. [50] For the first time cardiac arrhythmia in the form of symptomatic bradycardia described Ang C et al. [51] Capecitabine should be considered a drug with cardiotoxic potential even in the absence of prior cardiac history. It is believed that 5-Fu or its metabolites were responsible for cardiotoxicity after capecitabine administration. Coronary artery vasospasm, direct toxicity to the myocardium, thrombogenic effects and autoimmune phenomena have been proposed as plausible mechanisms. [52]

The mechanisms of cardiotoxicity of 5-Fu and capecitabine is shown in Table nr 3.

5-fluorouracil	coronary artery vasospasm, modulation of immune response, direct myocardial injury,
capecitabine	coronary artery vasospasm, direct toxicity to the myocardium, thrombogenic effects, autoimmune phenomena,

Table 3. The mechanisms of cardiotoxicity of 5-Fluorouracil and capecitabine

2.5 Cardiotoxicity of mitomycin C

There are reports of potentially cardiotoxic activity of mitomycin C. It is a antibiotic with antitumor cytotoxic activity. It is used in multi-drug regimens chemotherapy in the therapy of: stomach, colon, pancreatic, small cell lung, breast, cervical, advanced endometrial and squamous cell cancers of head and neck. [2]

2.6 Cardiotoxicity of cisplatin

2.6.1 Mechanism of antitumor action of cisplatin

Its effect is to create cross-linkages between adjacent strands of DNA and within the same thread. The formation of these cross-linkages prevents DNA replication and cell division. Also exerts influence on the metabolic functions of starting the process of cell apoptosis.

2.6.2 Clinical application of cisplatin

Cisplatin is a platinum substance and used in the treatment of many tumors (i.e. testicular cancer).

2.6.3 Mechanism of cardiotoxicity of cisplatin

Several cases of acute myocardial infarction after cisplatin therapy are reported. In a retrospective study 87 long term survivors of metastatic testicular cancer treated with cisplatin were evaluated for the occurrence of cardiovascular events. A significantly increase in cardiac events as well as an unfavorable cardiovascular risk profile were observed. [2]

Several factors have been suggested to be involved like vascular damage, alterations in platelet aggregation and hypomagnesemia. In experiments on human platelets cisplatin was able to trigger platelet aggregation and/or enhance thromboxane formation by platelets. Activation of an arachidonic pathway in platelets by cisplatin seemed to be involved. Raynaud phenomenon has been described in patients receiving cisplatin-based therapy. [2]

3. Cardiotoxicity of antineoplastic agents belonging to the so-called molecular targeted therapy

Molecular targeted therapy plays an increasingly important role in cancer therapy. This kind of treatment is also at risk of complications development including cardiac events. The most common symptoms associated with cardiac toxicity of molecular targeted therapy include hypertension, thromboembolic complications and dilated cardiomyopathy. Despite these symptoms treatment is better tolerated compared to other cytostatics. Most of the complications are reversible and respond to symptomatic treatment. Due to the fact that some of these drugs are used in combination with chemotherapy, reported side effects are the result of overlapping toxicities. Due to the relatively short experience with this type of therapy we cannot answer the question about the consequences of targeted therapy. [53]

This group of drugs of proven cardiac toxicity can be divided into:

- small molecule tyrosine kinase inhibitors (sunitinib, sorafenib, imatinib, lapatinib, dasatinib),

- proteasome inhibitors (bortezomib),
- monoclonal antibodies directed against the receptor or tyrosine kinase ligands (trastuzumab, bevacizumab). [54]

3.1 Small molecule tyrosine kinase inhibitors

This group of drugs bind to the part of the receptor complex, which is a tyrosine kinase. They are transmembrane proteins whose extracellular part acts as a both receptor and associated ligands at the same time [for example vascular endothelial growth factor (VEGF), platelet-derived (PDGF) etc.]. Intracellular domain of this protein has a catalytic activity. Key tyrosine kinases responsible for the pathogenesis of malignancy are associated with: vascular endothelial factor, FLT-1 and FLT-3-like tyrosine kinase fms, KDR kinase insert domain-containing receptor and for platelet-derived growth factor, stem cell factor receptor and RET-protonkogen. The emergence of the cancer cells will result from mutation and constant activation of these receptors.

Tyrosine kinase inhibitors block the activity of individual cells pathway-receptor signal transmission from membrane through cytoplasm to nucleus. They inhibit the activity of transcription factors and the expression of proteins responsible for fundamental processes of cancer cell development.

3.1.1 Sunitinib (SU 011248)

3.1.1.1 Mechanism of antitumor action of sunitinib

Sunitinib is an oral antiangiogenic small molekule tyrosine kinase inhibitor. It inhibits VEGFR-1 to VEGFR-3, stem cell factor receptor, platelet-derived growth factor receptor PDGFR-2-alfa and PDGFR-beta, RET, colony-stimulating factor-1 receptor, and fetal liver tyrosine kinase receptor 3 FLT-3. [55]

3.1.1.2 Clinical application of sunitinib

Sunitinib was approved by the European Medicines Agency (EMEA) for the treatment of advanced kidney cancer and / or metastatic kidney cancer and for the treatment of unresectable and / or metastatic GIST after failure of imatinib treatment due to resistance to imatinib or intolerant. [56]

3.1.1.3 Mechanism of cardiotoxicity of sunitinb

Sunitinib causes hypertension. In phase I clinical trials the incidence of CTC grade >=3 hypertension was 7.3%. [57] In single-agent phase II clinical trials with sunitinib the rates of grade 1-2 and grade 3 hypertension were 8.4% and 7.5% respectively. [58] In phase III clinical trials which established the efficacy of sunitinib in gastrointestinal stroma tumors (GISTs) and renal cell carcinoma grade 3 hypertension was more frequent in the sunitinib group than in the placebo group (3% versus 0%) or the interferon group (8% versus 1%). [59,60]

In phase I clinical trials of sunitinib two of 55 patients developed left ventricular dysfunction and heart failure. [57] In the phase II clinical trials of sunitinib in renal cell carcinoma 8.9% of patients developed a reduction in LVEF. [58] Grade 3 reductions in

LVEF were seen in a phase III trial of renal cell carcinoma. [60] In another retrospective analysis 11% of the patients with GISTs had heart failure and left ventricular dysfunction, 18% of patients had a myocardial infarction and/or asymptomatic elevations in troponin. [61] At the University of Stanford among 48 patients treated with sunitinib within 22-435 days after initiation of therapy in 7 (15%) patients experienced left ventricular III / IV grade according to the CTCAE (Common Terminology Criteria For Adverse Events). Despite the discontinuation of sunitinib heart failure maintained in 3 patients. Not without significance in this group of patients had a history of the burden from cardiovascular diseases as the 3 subjects had a history of heart failure, while another 2 patients were burdened with coronary artery disease. [62] In the University of Texas at 2.7% (6 / 224) of patients treated with sunitinib develop symptoms of heart failure during therapy in a one year. It is important that none of the reported patients prior to study entry had any heart disease. Five of the reported patients, who developed heart failure in the III and stage IV NYHA, required discontinuation of study drug. In one patient after the study drug dose reduction and after symptomatic treatment of heart failure symptoms subsided. [63]

Only a few cases of thromboembolic complications were reported. In phase I trials 2 of 55 patients developed myocardial infarction and pulmonary embolism. Two patients experienced pulmonary embolism and one experienced cerebrovascular accident in phase II studies. [57] These events were rare in phase III studies. [59,60]

The mechanism of cardiotoxicity associated with sunitinib therapy is not entirely clear. There are various hypotheses on this subject. It is shown that sunitinib induces the development of hypertension. It is not confirmed, that this is the way of the development of cardiac systolic dysfunction. Sunitinib inhibits cardiac PDGFR receptor. It is known that the number of active receptors and their signals transmitted to the interior have the great impact on survival of cardiomyocytes. Another hypothesis assumes that the mechanism of sunitinib cardiotoxicity may be related to inhibition of activating protein kinase (AMPK) and the kinase from the group of ribosomal S6 kinase (RSK 1). It is known that heart muscle cells require to function properly a large amount of energy. Thus they can be sensitive to inhibition of AMPK kinase, which acts as a regulating factor of the energy levels of ATP. Metformin used in diabetes, which activates AMPK kinase, does not protect against cardiac toxicity of treatment with sunitinib. [64] In addition, sunitinib treatment does not affect the level of cellular ATP. It is proven that the use of the dexrazoksan protection does not protect cardiomyocytes against the negative action of sunitinib. There are suggestions that the mechanism of toxicity of sunitinib is not associated with oxidative processes. Perhaps the non-selective inhibition of the kinase and blocking other pathways contribute to the development of drug-induced cardiotoxicity. [64]

3.1.2 Sorafenib (BAY 439006)

3.1.2.1 Mechanism of antitumor action of sorafenib

Sorafenib is an oral small molecule tyrosine kinase inhibitor designed to inhibit C-type Raf kinase (c-RAF), FLT-3, KIT, and B-type Raf kinase (b-RAF), VEGFR-2, VEGFR-3 and PDGFR. [55]

3.1.2.2 Clinical application of sorafenib

On the basis of multicenter clinical trials have shown that the use of sorafenib causes a statistically significant prolongation of progression-free survival of of patients with kidney cancer with prior ineffective immunotherapy.

3.1.2.3 Mechanism of cardiotoxicity of sorafenib

It has been proven that sorafenib may increase the risk of acute coronary syndrome, including myocardial infarction. An independent review of two studies by the FDA indicated that the incidence of ischemia/infarction was higher in the sorafenib group (2.9%) than in the placebo group (0.4%). [65] In another study the incidences of cardiac ischemia and infarction was significantly higher in the sorafenib arm (3% versus <1%). [66] In addition, sorafenib therapy may contribute to the occurrence of hypertension as with other targeted therapies that inhibit angiogenesis. In single-agent and combination phase I clinical trials of sorafenib the incidence of grade 3-4 hypertension was 3%. [67] In phase II studies with sorafenib 12% of patients developed grade 1-2 and 13.8% developed grade 3 hypertension. [68] In a phase III trial of sorafenib versus placebo in renal cell carcinoma hypertension was the most frequent serious adverse event but led to drug discontinuation in <1% of patients. The incidence of hypertension was significantly higher than in the placebo group: grade 2 10% versus 2% and grade 3-4 4% versus <1% , respectively. [66]

Similarly in a phase III trial in hepatocellular carcinoma patients grade 3 hypertension was more frequent in the sorafenib arm, but the difference did not reach the level of statistical significance. [69] Sorafenib-associated thrombotic events were infrequent (phase I trials, grade 3 thrombotic events 0.8%). No grade 3-4 thromboembolic events were noted in single-agent phase II studies or in phase III studies. [55] Perhaps the mechanism of cardiotoxicity of this drug results from inhibition of serine-threonine kinases RAF1 and BRAF. RAF1 inhibition blocks the activity of apoptosis signal regulating kinase 1 (ASK1) and mammalian stearin kinase 2 (MST2), which are involved in the mechanisms of formation of oxidative stress associated with tissue damage. It is still unclear the blockade by the sorafenib RAF1 or its effect on the signal transmission pathway of RAF1 to ASK1 and MST2 is at fault. [64]

3.1.3 Imatinib

3.1.3.1 Mechanism of antitumor action of imatinib

Imatinib strongly inhibits the tyrosine kinase Bcr-Abl, by blocking the transfer of a phosphate group from ATP molecules to the substrate protein tyrosine. Preventing this interaction blocks the ability to activate protein kinase transmitting proliferative signals to the nucleus and induces apoptosis of leukemia cells in patients with chronic myelogenous leukemia (CML) and acute lymphoblastic leukemia (ALL) with the Philadelphia chromosome. Imatinib also inhibits receptor tyrosine kinases platelet activation factor (PDGF), stem cell factor (SCF), Steel factor (c-KIT) and inhibits the cellular processes activated by PDGF and SCF. [70]

3.1.3.2 Clinical application of imatinib

This drug is used in the treatment of patient with chronic myelogenous leukemia and acute lymphoblastic leukemia.

3.1.3.3 Mechanism of cardiotoxicity of imatinib

O`Brief et al [71] reported ten individuals who developed severe congestive heart failure while on imatinib. They showed that imatinib-treated mice develop left ventricular contractile dysfunction. Transmission electron micrographs from humans and mice treated with imatinib showed mitochondrial abnormalities and accumulation of membrane whorls in both vacuoles and the sarco- (endo-) plasmic reticulum, findings suggestive of a toxic myopathy. With imatinib treatment, cardiomyocytes in culture show activation of the endoplasmic reticulum (ER) stress response, collapse of the mitochondrial membrane potential, release of cytochrome *c* into the cytosol, reduction in cellular ATP content and cell death. Retroviral gene transfer of an imatinib-resistant mutant of c-Abl, alleviation of ER stress or inhibition of Jun amino-terminal kinases, which are activated as a consequence of ER stress, largely rescues cardiomyocytes from imatinib-induced death. Thus, cardiotoxicity is an unanticipated side effect of inhibition of c-Abl by imatinib. [71]

In turn, international and randomized phase III study involving 1106 patients with newly diagnosed chronic myeloid leukemia with Philadelphia chromosome, who are in chronic phase, severe cardiac failure and left ventricular dysfunction was reported in 0.7% of patients receiving imatinib, compared to 0,9% of patients treated with interferon alpha (IFN) with cytosine arabinoside (Ara-C). However, in the IRIS study, after imatinib treatment of heart failure incidence was 1% of patients. [72]

Cardiac toxicity of imatinib may be due to inhibition by this drug tyrosine kinase c-Abl. It was confirmed that by the action of imatinib in response to oxidative stress occur:

- activation of the endoplasmic reticulum (ER),
- decreased mitochondrial membrane potential,
- release of cytochrome c into the cytosol,
- decrease in cell ATP and ultimately cell death. [71]

3.1.4 Dasatinib

3.1.4.1 Mechanism of antitumor action of dasatinib

Dasatinib is a potent inhibitor of the tyrosine kinase Bcr-Abl. Also it blocks a number of other tyrosine kinases, including compounds belonging to the families: scr, c-kit and PDGFR eEPHA 2.

3.1.4.2 Clinical application of dasatinib

This drug is used in the treatment of CML and Ph + ALL patients who had developed resistance to imatinib.

3.1.4.3 Mechanism of cardiotoxicity of dasatinib

There have been reports of congestive heart failure and cardiac arrhythmias in patients during dasatinib therapy. This medicine may also cause QT prolongation. Treatment with dasatinib may increase the risk of pulmonary arterial hypertension. Patients who reported the occurrence of pulmonary hypertension during treatment with dasatinib usually received other cardiotoxic drugs or suffered from other chronic diseases. In these patients improved hemodynamic and clinical parameters after discontinuation of treatment dasatinib was reported. [73]

3.1.5 Lapatinib (GW572016)

3.1.5.1 Mechanism of antitumor action of lapatinib

Lapatinib is an oral dual tyrosine kinase inhibitor selective for inhibition of EGFR/ErbB1 and HER2/ErbB2.

3.1.5.2 Clinical application of lapatinib.

This small molecule represents one of the most promising target therapies in breast cancer that overexpressed HER2. It is used in trastuzumab-refractory breast cancer.

3.1.5.3 Mechanism of cardiotoxicity of lapatinib

Perez et al. reviewed the cardiotoxicity data of lapatinib in 3558 patients, including 1674 breast cancer patients, already treated with the drug alone or in combination with other agents. A total of 1090 patients had >6 months exposure to lapatinib. Evaluation of cardiac left ventricular ejection fraction (LVEF) was done every 8 weeks while patients were receiving therapy, in addition to follow-up for any cardiac clinical events. A preliminary analysis of patients treated with lapatinib to date revealed that incidence of symptomatic

- Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of several malignancies, converting lethal diseases into manageable, if not curable, chronic diseases. This is essential to limit toxicities of these agents.
- The goal of tumor-cell killing by TKIs must be balanced against cardiotoxicity, because in some instances tumor cell death and preservation of cardiomyocyte health may be mutually exclusive.
- Cardiomyocytes are contractile and have an extremely high demand for ATP. As a result, they might be particularly susceptible to agents that perturb mitochondrial function, either as a primary or secondary effect. Therefore, alterations in mitochondrial function could have a role in the cardiotoxicities of some currently approved agents.
- Very few clinical trials have examined cardiotoxicities of TKIs in a prospective fashion with predefined cardiac endpoints, including left ventricular function. Therefore, there is a wide gap in our knowledge regarding the types, and risk of, cardiotoxicity for most of these agents.
- Some current kinase targets in cancer are not expressed in cardiomyocytes. Therefore have little or no direct role in cardiomyocyte survival. The current generation of TKIs is inherently non-selective, and the purposeful design of multitargeted TKIs might allow a single agent to be more effective, and to be used in more types of cancer, but with this comes an increased risk of cardiotoxicity. In some cases this will probably be due to inhibition of 'bystander' targets that are not essential for the killing of tumour cells but that are involved in cardiomyocyte survival.
- Identification of the kinase responsible for cardiotoxicity of an agent is important for future drug design. Future kinases should avoid this kinase. Thus, greater selectivity of individual agents may require the use of more agents to treat a particular cancer, but cardiotoxicity as an 'off-target' effect should be minimized.

Table 4. Tyrosine kinase inhibitors- SUMMARY

and asymptomatic decreased LVEF among 1674 breast cancer patients was 1.3% and was also 1.3% among 1453 patients with non- breast malignancies. Lapatinib- associated LVEF decrease was symptomatic in 0.1%, generally reversible/nonprogressive. Average duration of LVEF decrease was 40 days. The other studies conducted so far showed that the cardiotoxicity associated with lapatinib is not severe, is reversible, and usually patients can continue lapatinib therapy, when symptomatic treatment has been started. [54]

3.2 Bortezomib

Recent case reports provide alarming signals that treatment with bortezomib might be associated with cardiac events.

3.2.1 Mechanism of antitumor action of bortezomib

Bortezomib is a reversible proteasome inhibitor.

3.2.2 Clinical application of bortezomib

It is used in treatment of patients suffering from multiple myeloma or mantle cell lymphoma.

3.2.3 Mechanism of cardiotoxicity of bortezomib

Nowis et al. [74] reported that bortezomib treatment leads to left ventricular contractile dysfunction in rats manifested by a significant drop in left ventricle ejection fraction. It is important that in this study rats were not treated with other drugs. Dramatic ultrastructular abnormalities of cardiomyocytes, especially within mitochondria, were accompanied by decreased ATP synthesis and decreased cardiomyocyte contractility. [74] Bortezomib induced cardiac effects seem to be reversible. The risk of cardiotoxicity after bortezomib is higher in patients which have previously cardiac problems or being concomitantly treated with other chemotherapeutics including cardiotoxic anthracyclines. In a recent phase III clinical study of bortezomib was used in combination with pegylated liposomal doxorubicin, LVEF ejection fraction was reported to decrease in 7% of patients treated with bortezomib. [75] In another clinical study, grade 3 to 4 cardiac heart failure was reported in 2 cases (one fatal) receiving bortezomib in combination with doxorubicin. [76]

3.3 Monoclonal antibodies directed against the receptor or tyrosine kinase ligands

3.3.1 Trastuzumab

3.3.1.1 Mechanism of antitumor action of trastuzumab

Trastuzumab is a monoclonal antibody selectively connecting to the extracellular domain of HER-2 receptor, which belongs to the family of epidermal growth factor receptors. Overexpression of this receptor is found in approximately 20-25% of breast cancers. It is presence is associated with poor prognosis and shorter overall survival time. [22]

3.3.1.2 Clinical application of trastuzumab

Trastuzumab improves response rate and survival in women with metastatic breast cancer with known overexpression of the HER-2 receptor. Also the use of trastuzumab

concurrently with adjuvant chemotherapy significantly improves the relapse-free survival and overall survival in women with overexpressing HER-2 receptor in localized form of breast cancer. [22]

3.3.1.3 Risk factors for cardiotoxicity after treatment with trastuzumab

The risk factors associated with trastuzumab cardiotoxicity include:

- history of hypertension,
- diabetes,
- obesity,
- older age,
- past radiotherapy prior therapy with anthracyclines.

It was proven that the risk of cardiomyopathy after trastuzumab (as opposed to anthracycline antibiotics) does not depend on the total dose of drug. Contrast, cardiac dysfunction associated with trastuzumab therapy is completely reversible after discontinuation of the drug and after symptomatic treatment and leaves without residual effects in the structure of cardiac muscle. [77]

3.3.1.4 Mechanism of cardiotoxicity of trastuzumab

Cardiotoxicity associated with trastuzumab was analyzed only in the phase III trials, sporadic cases relate to assessment of phase II trials, because nobody knows whether this drug may cause clinically significant cardiac complications. No patients were monitored in terms of efficiency of the cardiovascular system during trastuzumab therapy.

Cardiac complications, grade IV NYHA (New York Heart Association) was observed in 2% of patients treated with trastuzumab in the first line, in 4% of patients treated with trastuzumab because of resistance to previous treatment, in 2% of patients treated with concomitant paclitaxel and trastuzumab (compared to 1% of patients the group receiving paclitaxel alone) and in 16% of patients receiving chemotherapy: adriamycin with cyclophosphamide (AC) plus trastuzumab (compared to 4% in the group receiving chemotherapy alone AC). Symptoms of heart failure occurred in 75.5% of patients (83 in the group of 110 patients). In 79% of cases symptomatic treatment of heart failure has proved effective. [77]

Based on 7 studies: phase II and III, Cardiac Review and Evaluation Committee (CREC) conducted a retrospective analysis of cardiac events associated with trastuzumab therapy. One analysis was based on international study 222 women who received trastuzumab in the second or third line treatment of metastatic breast cancer. Patients were previously treated with anthracyclines (94% women), taxanes (67% women), radiotherapy (71% women), hormonal therapy (57% women). Cardiac complications were seen in 10 patients (4.7%), including 3 patients after treatment with trastuzumab. 9 patient out of all who develop complication (n=10) had been treated with anthracylines previously. Most of the cardiac complications in this study were clinically significant. There was one death following a ventricular arrhythmia, in a patient after previous treatment with anthracyclines with reduced baseline left ventricular ejection fraction. [78]

Another study conducted by CREC concerned randomized, international phase III study comparing trastuzumab in combination with chemotherapy to chemotherapy alone in 469 patients with metastatic breast cancer. The symptoms of cardiotoxicity were observed in

27% of patients who received trastuzumab with anthracyclines and cyclophosphamide compared to 8% of patients after treatment with chemotherapy alone (anthracycline and cyclophosphamide without trastuzumab). In 13% of patients treated with paclitaxel with trastuzumab cardiac complications occurred. Continuation of trastuzumab did not affect the severity of dysfunction of the cardiovascular system in most patients. The symptomatic treatment was effective. [78]

Further analysis concerned three trials [338 patients] where trastuzumab monotherapy was used. It was estimated that the risk of cardiotoxicity associated with trastuzumab was 4%. 3% of patients had grade 3 and 4 toxicity according to Common Toxicity Criteria (CTC). [78]

Mechanism of cardiotoxicity induced by trastuzumab is still not fully clear. But role of inhibition of normal cardiac repair pathways by this drug seem to be probable. Her-2 heterodimerizes to Her-4, leading to autophosphorylation of the Her-2 tyrosine kinase domain. [79] This complex, which is the antitumor target of trastuzumab, is also active in cardiac repair. The complex is activated by neuregulin 1, which is secreted in paracrine fashion by cardiac endothelial cells that are under stress. [79] Activation of the complex leads to multiple downstream effects. In turn they lead to hypertrophy of cardiac myocytes in vivo. In mice, deletion of Her-2 results in a dilated cardiomyopathy. [80] Chien proposed a model in which various types of cardiac stress such as mechanical strain, anthracyclines, or hypoxia trigger two competing pathways of cardiac myocyte survival (mediated by neuregulin-1 or gp 130 cytokines) or apoptosis. The clinical outcome depends on which process prevails. In this model, treatment with trastuzumab blocks the survival pathway by preventing Her-2/Her-4 heterodimerization, thus shifting the balance to apoptosis. The result is decreased cardiac contractility and CHF. [81]

Mechanism for inducing cardiotoxicity by trastuzumab is presented in Table nr 5.

• by the presence of HER-2 receptor on cardiomyocytes,
• blocks the cardiac survival pathway by preventing Her-2/Her-4 heterodimerization,
• induced apoptosis of cardiomyocytes,
• cased hypertrophy of cardiac myocytes,

Table 5. Mechanism of cardiotoxicity of trastuzumab

3.3.2 Bevacizumab

3.3.2.1 Mechanism of antitumor action of bevacizumab

Bevacizumab is a recombinant humanised IgG monoclonal antibody specifically binds to vascular endothelial growth factor (VEGF) and blocking its connection to the membrane receptor and thereby inhibits the process of neoangiogenesis.

3.3.2.2 Clinical application of bevacizumab

Bevacizumab is adjunct to cytotoxic drug combination. It is approved for use in colon, lung, renal and breast cancer.

3.3.2.3 Mechanism of cardiotoxicity of bevacizumab

Based on the research phase I and II found that the possible side effects of bevacizumab are:

- bleeding,
- thromboembolism,
- proteinuria,
- hypertension.

The presence of hypertension was reported in 5-7% of patients participating in clinical trials. It was also observed [in rare cases] development of encephalopathy associated with hypertension and subarachnoid haemorrhage. Patients after treatment with anthracyclines and radiotherapy are at increased risk for cardiac complications during or after treatment with bevacizumab. In patients previously treated with anthracyclines followed by mediastinal radiotherapy, the incidence of left heart failure was about 4%. When anthracyclines and radiotherapy were used at the same time heart failure was observed in 14% of patients. [54]

In a randomized study breast cancer patients receiving paclitaxel with bevacizumab compared to patients receiving paclitaxel alone the risk of hypertension 3 and 4 level rose to about 15%, thromboembolic events up to about 2.5%, proteinuria to about 3.1% and cardiac function the left ventricle to 1.4%. One patient receiving bevacizumab with paclitaxel died of a myocardial infarction. [54]

4. Cardiotoxicity of anagrelide

1. Mechanism of antitumor action of anagrelide.

Anagrelide works by inhibiting the maturation of platelets from megakaryocytes. The exact mechanism of action is unclear, although it is known to be a phosphodiesterase inhibitor. It is a potent inhibitor of phosphodiesterase-II. It inhibits PDE-3 and phospholipase A2.

2. Clinical application of anagrelide.

This medicine is a standard treatment of thrombocythemia in chronic myeloproliferative disorders: essential thrombocythaemia (ET), polycythemia vera (PV) and bone marrow fibrosis.

3. The mechanism of cardiotoxicity of anagrelide.

The mechanism of cardiotoxicity of this drug is not fully known. It may be due to medicine`s positive inotropic effect or consequence of vasodilatation and tachyarrhythmia induced by anagrelide. During the treatment following can occur: palpitations and tachycardia, less common- congestive heart failure, hypertension, arrhythmia, atrial fibrillation and the occasional- angina, myocardial infarction, cardiomegaly, cardiomyopathy, pericardial effusion, and orthostatic hypotension. [82]

Anagrelide was found as a cause of cardiomyopathy in 2000 at the Mayo Clinic [Rochester, USA]. The data were collected from 434 patients suffered from essential thrombocythaemia and polycythemia vera. Investigators confirmed by echocardiography the development of idiopathic cardiomyopathy during treatment of these chronic myeloproliferative disorders with anagrelide in 11 patients. The decrease in LVEF was significant from 35% (two persons) to 10% (one person). Discontinuation of treatment with anagrelide resulted in an increased LVEF. [82]

Cardiotoxicity of anagrelide also confirmed case of 50-year-old man diagnosed with essential thrombocythaemia. Due to the increasing resistance to first-line treatment the patient was treated with anagrelide in a dose gradually increasing up to 2.5 mg twice a day. The patient developed clinical features of congestive heart failure, NYHA IV. LVEF was 18%. ECG findings were typical for myocardial ischemia but troponin T level was normal. Coronary angiography was performed revealing normal in which the coronary arteries. Treatment of anagrelide was stopped, hydroxyurea therapy was started again. Patients received symptomatic therapy of heart failure: diuretics and ACE-inhibitors with good response. Hydroxyurea therapy once again proved to be ineffective. Doctors were decided to join hydroxyurea of anagrelide at a reduced dose 0.5 mg twice a day. Modification of treatment was effective, the level of platelets decreased to the normal limits, the symptoms of heart failure was absent. ECHO, made by 2 and 8 months after starting treatment with anagrelide [low doses] and hydroxyurea, showed increasing LVEF from 40 to 50%. [83]

These observations confirm that the use of anagrelide is not absolutely safe to the cardiovascular system. Cardiomyopathy, during anagrelide treatment is rare but clinically significant. Therefore, patients with a history of heart disease should be treated with anagrelide with caution, when potential benefits exceed risk of this kind therapy. [82,83]

Mechanism of cardiotoxicity associated with the action of anagrelide is showen in Table nr 6.

• by positive inotropic effects, • by vasodilatation, • by tachyarrythmias,

Table 6. The mechanism of cardiotoxicity of anagrelide

5. Cardiotoxicity of High Dose Chemotherapy (HDC) followed by Hematopoietic Stem Cell Transplantation (HSCT)

Hematopoietic stem cell transplantation (HSCT) has now become the treatment of choice for large number of malignant and non-malignant diseases. Cardiac complications may result from high-dose chemotherapy or irradiation administered during the conditioning phase of bone marrow and blood stem cell transplantation (BMT). Cardiac complications of high-dose cyclophosphamide and total body irradiation (TBI) or other intensive conditioning regimens administered prior to bone marrow and stem cell transplantation (BMT) have been well documented. Clinically, patients present with congestive heart failure and pancarditis. Hemorrhagic perimyocarditis with endothelial damage and microthrombi in capillaries as well as acute fibrinous pericarditis. Several other cytotoxic drugs such as busulfan, carmustine or cytarabine used in pre-BMT regimens may cause significant cardiotoxicity. Acute myocardial infarction and various cardiac arrhythmias including cardiac arrest as a consequence of infusion of cryopreserved marrow have been reported during the acute phase of BMT. Pretreatment with anti-tumor antibiotics including anthracyclines and prior mediastinal irradiation may increase the risks of adverse cardiac sequelae after BMT, but identification of the risk factors and effective strategies for cardiologic prescreening have not been well established. Although cardiac complications associated with BMT have been documented in several series, the incidence of reported cardiotoxicity has varied among investigators, probably reflecting patient

selection, differences in BMT preparative regimens and lack of universal grading system for cardiotoxic events. [84-87]

Cardiac complications associated with exposure to the conditioning factors can be acute, with a relatively short or long period of latency after HSCT. [84-87]

To assess the frequency of clinically serious cardiac toxicity related to the acute phase of bone marrow transplantation (BMT), investigators from University of Minnesota retrospectively examined life-threatening or fatal cardiotoxicity identified using the complications records of their transplant center clinical database. All serious cardiac toxicity events within 100 days of BMT except those attributable to septic shock, pneumonitis or multi-organ failure were reviewed. During the first 100 days after transplantation 628 cardiac complications experienced and divided by four-level scale cardiac toxicity [86]:

- Stage I- asymptomatic cardiomegaly, mild ECG changes, not requiring treatment, asymptomatic stroke in the pericardium,
- Stage II- moderate changes in the ECG, which require and well respond to routine treatment, congestive heart failure responsive to afterload reduction in the treatment of diuretics and digitalis, pericarditis,
- Stage III: severe abnormalities in the ECG with no or partial response to medical intervention, congestive heart failure, requiring drugs with isotropic, cardiogenic shock, reducing the voltage wave QRS&> 50%, pericardial tamponade.
- Stage IV- death following cardiac toxicity.

Of 2821 BMT patients at the University of Minnesota between 1977 and 1997, 26 were identified as having suffered major or fatal (n = 13) cardiotoxicity (0.9%, 19 adults and seven children). Rapidly progressive heart failure resulted in death of 11 patients, one patient had fatal pericardial tamponade, and one had an acute ventricular fibrillation arrest. The remaining 13 patients (50%) had life-threatening cardiotoxicity including four patients with pericardial tamponade and nine patients with cardiac arrhythmias. Overall, we observed that acute, major cardiotoxic events attributable to BMT are uncommon, occurring with a frequency of 1%. These data suggest that with appropriate pre-transplant clinical evaluation, high-dose cyclophosphamide and irradiation in the BMT preparative phase does not result in frequent, clinically relevant short-term cardiac toxicity. [86]

The most common late complications of HSCT include valvular dysfunction, conduction disturbances, pericarditis and cardiomyopathies. Are also observed vascular complications, which include: coronary heart disease, cerebral vascular dysfunction and disease. [84-87]

Investigators from City of Hope National Medical Center [87] examined the independent roles of pre-hematopoietic cell transplantation (HCT) therapeutic exposures, transplantation-related conditioning, and comorbidities (pre- and post-HCT) in the development of late congestive heart failure (CHF) after HCT. This was a nested case-control design. Individuals with late CHF (diagnosed 1 year after HCT) were identified from a cohort of 2,938 1 year survivors who underwent transplantation at City of Hope National Medical Center, Duarte, CA. This cohort formed the sampling frame for selecting controls (without CHF) matched for age and year of HCT, donor source (allogeneic v autologous), and length of follow-up. Sixty patients with late CHF were identified; median age at HCT was 45.3

years (range, 16.6 to 68.6 years); median time to CHF was 3.0 years (range, 1.03 to 18.9 years); 68% received autologous HCT. Median ejection fraction was 36.9% (range, 15% to 53%). Compared with matched controls (n = 166), patients with late CHF received more cycles of pre-HCT chemotherapy (8.6 v 4.9 cycles; P= 0.01), had greater body mass index at HCT (28.4 v 26.2 kg/m^2; P= 0.01), greater lifetime anthracycline exposure (285.3 v 175.6 mg/m^2; P= 0.01), and were more likely to have multiple chronic comorbidities (30.0% v 13.9%; P= 0.01). Multivariable analysis revealed number of pre-HCT chemotherapy cycles (odds ratio [OR] 1.2; P= 0.01), anthracycline dose 250 mg/m^2 (OR 3.2; P= 0.05), and two or more chronic comorbidities (OR 4.3; P= 0.01) to be independently associated with late CHF. Pre-HCT exposure to anthracyclines and presence of comorbidities are primarily risk associated with late CHF after HCT. Conditioning-related therapeutic exposure does not contribute significantly to the risk. These results form the basis for identifying high-risk individuals for targeted surveillance, as well as developing preventive strategies in the form of aggressive management of comorbidities. [87]

Considering all of the above the important factors affecting the occurrence of cardiotoxic high dose chemotherapy complications include exposure to high doses of cyclophosphamide, total body irradiation, prior anthracycline therapy, the presence of dimethyl sulfoxide (DMSO) in intravenous products, infectious complications associated with neutropenia. The risk of cardiac complications after HSCT is also influenced by patient age, type of therapy applied and previous medical history. [84]

Dimethyl sulphoxide (DMSO) is cells protective factor, preventing the crystallization of water and damage to cell membranes collected stem cells, which are subjected to freezing in liquid nitrogen at temperatures below -120 degrees C. Cardiotoxicity associated with DMSO may result in hypotension, requiring fluid infusion or even inotropic drugs. Ones also reported cardiac arrhythmias such as atrial fibrillation, or bradycardia, and incidents of acute coronary syndromes. Cardiotoxicity associated with DMSO is rare. Wether DMSO is responsible for these has been questioned. [84,85] Recent reports of similar acute cardiac events despite DMSO depletion have led to the suggestion that perhaps the complications seen following infusion may be more a product of the amount of infused granulocytes, rather than DMSO. [84]

Infectious complications during early post-transplant neutropenia or prolonged immunosuppression for GVHD prophylaxis are common problems following HSCT. Overwhelming sepsis can lead to cardiopulmonary failure, necessitating prolonged intubation and cardiac inotropic support, potentially causing subclinical cardiotoxicity or other end-organ compromise that may not be evident until years following HSCT. [84]

The Tichellis study [84] provided preliminary evidence for an association between GVHD and the development of arterial disease. There are emerging data to suggest that chronic GVHD could play a role in the development of cardiovascular disease. Cardiac side effects of chronic GVHD, while rare, likely occur as a result of direct organ lymphocytic infiltration. Increased levels of circulating tumor necrosis factor alfa [TNF alfa] may impair muscle electrical activity and compromise myocardial contractility. Furthermore, increased amounts of inflammatory markers, such as TNF alfa and interleukin-6, could perpetuate endothelial injury, contributing to premature arterial events in long-term survivors after allogeneic HSCT. Treatment of GVHD is not without cardiovascular consequences.

Prolonged treatment with calcineurin inhibitors and steroids can lead to myocardial hypertrophy, as well as increase the likehood of cardiovascular disease risk factors such as hypertension, diabetes, and renal insufficiency. [84]

6. Carditoxicity of radiotherapy

In anticancer treatment, radiotherapy plays an important role. It can also damage the heart muscle. Due to the location of the heart in human body, mediastinal radiotherapy poses the highest risk of cardiac complications. This form of treatment is commonly used in lymphoma, breast, esophageal and lung cancers. In connection with the expected long period of survival of patients with Hodgkin lymphoma and breast cancer the risk of complications from cardiovascular diseases is the highest. The maximum potential safe dose of ionizing radiation on the heart area are as follows [88]:

- approximately 60 Gy when 25% or less heart volume is irradiated,
- about 45 Gy, while 65% of the volume of the heart is irradiated with a standard fractionation at 2 Gy per day.

Early cardiac complication after radiation therapy is acute pericarditis, which usually occurs within a few weeks after treatment. The most common late effect of radiotherapy on cardiovascular system is coronary artery disease. It usually appears within 10-15 years after radiation. Ones have been shown that ionizing radiation can initiate or accelerate the atherosclerotic process, this phenomenon refers mainly to people with other risk factors for cardiovascular disease. On others cardiac structures radiotherapy also has a negative effect, but to a lesser extent. It may lead to development of restrictive cardiomyopathy, cardiac diastolic dysfunction, impaired contractile function [that occurs after mated treatment with anthracyclines], aortic stenosis, QT prolongation, persistent tachycardia [damage of autonomic nervous system]. [88]

Risk factors for acute or chronic cardiac complications after radiation therapy include [88]:

- irradiated volume of the heart (cardiac risk is proportional to the irradiated volume of the heart),
- patient age (younger age at the time of exposure to ionizing radiation is a risk factor for vascular disease),
- time of exposure (the majority of published reports that the need for a minimum of 10 years to the risk of death from heart attack increased above 10%),
- dose and technique of application of ionizing radiation (it is considered that the total radiation dose in the case of mediastinal radiotherapy, increasing the risk of cardiovascular disease is> 35-40 Gy, whereas a fractional dose> 2 Gy per day) and
- prior chemotherapy (especially anthracycline-based regimens).

7. Cardiotoxicity of antagonists of 5-HT3 receptor

Potentially cardiotoxic drugs, inevitably associated with oncology therapy, are also antagonists of 5-HT3 receptor. Chemotherapy, especially given in high doses causes of nausea and vomiting, which are very burdensome for the patient with neoplastic disease. The mechanism of vomiting is the release of large amount of serotonin, stimulating 5-HT3

receptors located on nerve endings centripetal parasympathetic system. Parasympathetic system also innervates the heart muscle, which explains the cause of the cardiac complications associated with this class of drugs. [89]

Results of the review of clinical trials with MEDLINE database from the period 1963-2002 for cardiotoxicity antagonists 5-HT3 receptor were as follows [89-91]:

- ECG changes (PR, QRS, QT, QTc, JT) were small, reversible, clinically insignificant and dependent on the selected group of patients,
- ECG changes occurred most frequently between 1 and 2 hours after administration of dolasetron, ondansetron and granisetron and returned to normal within 24 hours, no evidence of acute, clinically significant cardiac complications.

Based on these data it was concluded that the benefits of this class of drugs greatly outweigh their adverse effects on the cardiovascular system. [91]

Considering the high risk of cardiac complications due to oncological treatment, it is important to establish standards of conduct with patients undergoing cancer therapy proven to cardiac toxicity.

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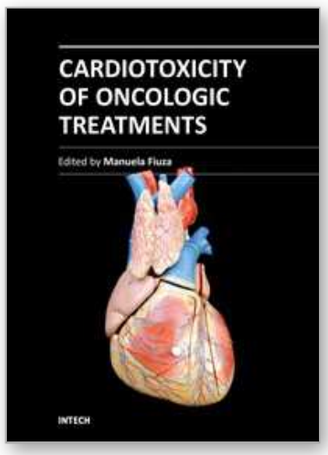

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The possibility of getting a cardiovascular disease or cancer increases with advancing age. At the same time, relevant improvements in cancer therapy have resulted in the improvement of quality of life and the increasement of the survival rate of such patients. As a result we have larger number of patients that experience the cardiac side effects of chemotherapy. The extent of cardiotoxicity is variable, depending on the type of drug used, combination with other drugs, prior mediastinal radiotherapy and the presence of cardiovascular risk factors or history of heart disease. Early detection of the patients proneness for developing cardiotoxicity is the key issue to decrease morbidity and mortality. It also facilitates more tailored therapeutic interventions. Therefore, the collaboration and interaction of cardiology and oncology may contribute to reducing the cardiovascular adverse effects and improving the results in the treatment of patients with cancer.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
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