

ANTHRACYCLINE-INDUCED CARDIOTOXICITY

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Summary: Anthracycline antibiotics are among the most effective and widely used antineoplastic drugs. Their usefulness is limited by a cumulative dose-related cardiotoxicity, whose precise mechanisms are not clear as yet. The principal role is possibly exerted by free oxygen radicals generated by „redox-cycling“ of anthracycline molecule and/or by the formation of anthracycline-ferric ion complexes. The iron catalyzes the hydroxyl radical production via Haber-Weiss reaction. The selective toxicity of ANT against cardiomyocytes results from high accumulation of ANT in cardiac tissue, appreciable production of oxygen radicals by mitochondria and relatively poor antioxidant defense systems. Other additional mechanisms of the anthracycline cardiotoxicity have been proposed - calcium overload, histamine release and impairment in autonomic regulation of heart function. The currently used methods for an early identification of anthracycline cardiotoxicity comprise ECG measurement, biochemical markers, functional measurement and morphologic examination. Among a plenty of studied cardioprotective agents only dexrazoxane (ICRF-187) has been approved for clinical use. Its protective effect likely consists in intracellular chelating of iron. However, in high doses dexrazoxane itself may cause myelotoxicity. This fact encourages investigation of new cardioprotectants with lower toxicity. Orally active iron chelators and flavonoids attract more attention. Modification of dosage schedule and synthesis of new anthracycline analogues may represent alternative approaches to mitigate anthracycline cardiotoxicity while preserving antitumour activity.

Key words: Anthracyclines; Cardioprotection; Cardiotoxicity; Daunorubicin; Dexrazoxane; Doxorubicin; Free radicals; Iron chelators

Abbreviations:

| | | | | | |
|------|------------------------------|--------|-------------------------|------|------------------------|
| ADR | - adriamycin | DOX | - doxorubicin | LV | - left ventricle |
| ANP | - atrial natriuretic peptide | ECHO | - echocardiography | LVEF | - LV ejection fraction |
| ANT | - anthracycline(s) | GSH | - reduced glutathione | PFR | - peak filling rate |
| BNP | - brain natriuretic peptide | GSH-Px | - GSH peroxidase | RUB | - rubidomycin |
| cTnT | - cardiac troponin T | hr | - hour(s) | SOD | - superoxide dismutase |
| DAU | - daunorubicin | CHF | - chronic heart failure | wk | - week(s) |

Introduction

Since the late 1960's the anthracycline antibiotics (ANT) doxorubicin (DOX; also known as adriamycin - ADR) and daunorubicin (DAU; also rubidomycin - RUB) have been among the most effective and widely used antineoplastic agents (39). Especially DOX is active against a wide range of tumours, including acute leukaemias and lymphomas, sarcomas, malignant neoplasms of bladder, breast, lung, ovary, stomach and thyroid (51). Apart from the adverse effects that are common to many other cytotoxic agents, (i.e. gastrointestinal disturbances - nausea and vomiting, alopecia, haematopoietic suppression), the clinical usefulness of ANT is largely limited by a cumulative dose-related cardiomyopathy,

resulting in congestive heart failure (30). This may be fatal in as many as 60% of patients who develop it (64).

Much effort has been devoted to elucidate the mechanisms underlying the above-mentioned serious toxic effect of ANT. In spite of this the precise mechanisms have not been solved as yet. Below we review the anthracycline-induced chronic cardiotoxicity: Its proposed mechanisms, the methods for early detection and approaches to mitigate it.

1. Pathogenesis of anthracycline-induced cardiotoxicity

Treatment with ANT may be associated with various types of cardiotoxicity (13):

- *acute toxicity* is preferentially related to rapid i.v. administration and is manifested by vasodilatation, hypotension and cardiac dysrhythmias
- *subacute toxicity* is uncommon, it develops early in the course of therapy and is characterized by myocarditis and pericarditis
- *chronic toxicity* is the most common form of ANT-induced cardiotoxicity and is manifested by chronic dilated cardiomyopathy, which develops late in the course of therapy, or shortly after its termination. This review deals primarily with this type of cardiotoxicity.
- *delayed toxicity* has been recently found in the survivors of childhood cancers. The delayed cardiomyopathy develops at periods of time ranging up to 10-15 years after the termination of treatment. Little is known about the cause, outcome, prevention or treatment of this form of cardiotoxicity. In contrast to chronic *dilated* cardiomyopathy, the delayed form is characterized by *restrictive* process with decreased left ventricular (LV) compliance and a small thin left ventricle (35).

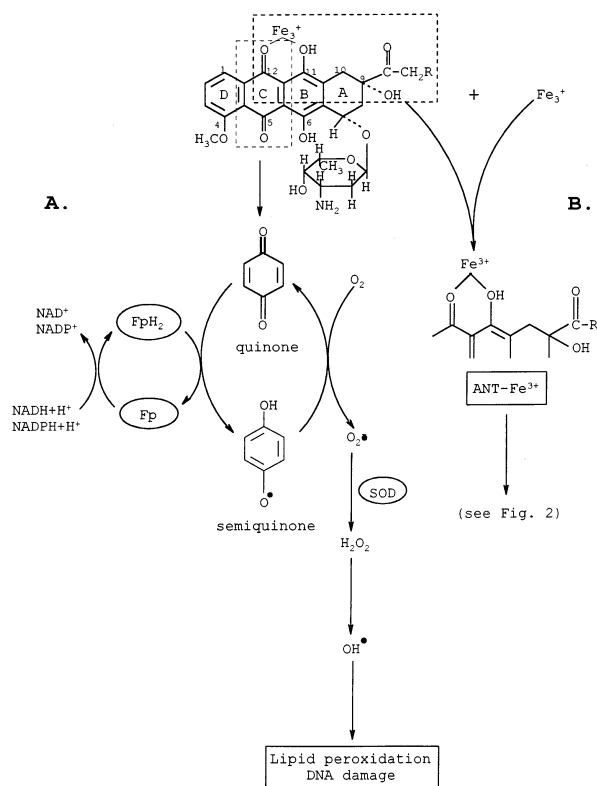


Fig. 1: Formation of oxygen free radicals by anthracyclines (R= -OH doxorubicin; -H daunorubicin). 1A. „Redox cycling“ of the quinone moiety (ring C) of the anthracycline molecule. 1B. Formation of the anthracycline-iron (ferric ion) complex. The following steps in oxygen free radicals production - see fig. 2. Fp - flavoprotein enzymes (oxidized form), FpH₂ - flavoprotein enzymes (reduced form), SOD - superoxide dismutase.

1.1. Free-radicals dependent mechanisms

The generation of free radicals has been experimentally demonstrated both *in vitro* (34,50) and *in vivo* (36). The two main pathways responsible for free radicals generation by ANT comprise the redox-cycling of ANT molecule and formation of ANT-ferric ion complexes.

Redox-cycling of ANT is related to the presence of quinone moiety in the ANT molecule - see fig. 1A. The quinone structure of ANT permits this compound to act as an electron acceptor, the transfer being mediated by flavoprotein enzymes including mitochondrial NADH dehydrogenase, microsomal NADPH-cytochrome P-450 reductase, or cytochrome b₅ reductase. The semiquinone form reacts with oxygen to generate superoxide radical O₂^{•-}, at the same time quinone form being regenerated. The dismutation of O₂^{•-} to H₂O₂ is catalyzed by superoxide dismutase (SOD), or may occur spontaneously. H₂O₂ is a relatively stable molecule. The generation of OH[•] from H₂O₂ is dependent on catalytic role of trace elements, especially iron:

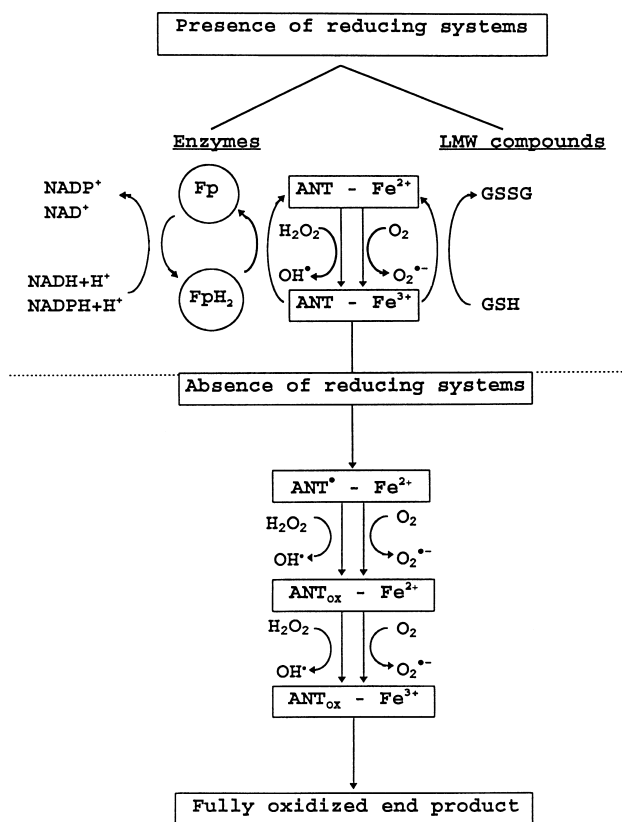
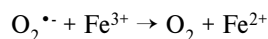
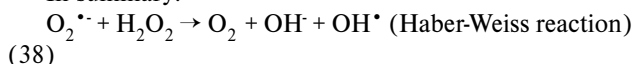


Fig. 2: Oxygen free radicals production by the anthracycline-iron complex (ANT-Fe³⁺, ANT-Fe²⁺). Further explanation in text. Fp - flavoprotein enzymes (oxidized form), FpH₂ - flavoprotein enzymes (reduced form), LMW compounds - low-molecular-weight compounds, ANTO_x-Fe³⁺ - the oxidized complex anthracycline-ferric ion.



In summary:



The highly reactive hydroxyl radical OH^\bullet can directly damage DNA and could lead to lipid peroxidation. This results in production of a great number of relatively stable (compared with short-lived radicals), diffusible aldehydes (e.g. malondialdehyde, 4-hydroxyalkenals, alkanals, etc.). The cytotoxic aldehydes are extremely reactive, they can diffuse within the cell, or even cross the plasma membrane and attack macromolecular targets far from the site of their origin. They can act as „second cytotoxic messengers“ (36).

The second, even more important, pathway of free radicals production consists in formation of ANT-ferric ion (ANT-Fe^{3+}) complex, see fig. 1B and fig. 2. The ANT-Fe^{3+} complex can be reduced to ANT-Fe^{2+} either enzymatically by various flavoproteins (compare with reduction of quinone form of ANT to semiquinone), or by low-molecular-weight reducing agents, e.g. by GSH, cystein, etc. In the absence of reducing systems, the complex ANT-Fe^{3+} can reduce its iron in expense of intramolecular oxidation of ANT molecule until the fully oxidized end product of ANT is reached (30). The complex ANT-Fe^{2+} can react with O_2 and H_2O_2 to generate $\text{O}_2^{\bullet-}$ and OH^\bullet , resp.

The question arises why the cardiomyocytes are so susceptible to the oxidative stress produced by ANT in comparison with other tissues. This may reflect several reasons:

- high accumulation of ANT was observed in chick embryo heart cells in comparison with the liver cells and murine L5178Y lymphoblasts (38)
- cardiac cells are rich in mitochondria. It is generally accepted that these organelles are important target of ANT molecular effects and that cardioselective mitochondrial dysfunction is implicated in the chronic ANT cardiotoxicity (8,34,54). The following steps seem to cause depression of energy metabolism in cardiac tissue: After one electron reduction of the parent *hydrophilic* ANT molecule a cleavage of the sugar residue occurs. Accumulation of the *lipophilic* ANT aglycon in the inner mitochondrial membrane diverts electrons from the regular pathway to electron acceptor (O_2) with subsequent production of oxygen free radicals (fig. 1). The radicals affect the integrity of energy-linked respiration. Moreover, the important role is exerted by the exogenous NADH dehydrogenase, which is cardioselective (18,46). Unlike heart mitochondria, intact liver mitochondria are lacking the NADH-related pathway of reducing equivalents from the cytosol to the respiratory chain. As a result the liver mitochondria do not generate significant amounts of ANT semiquinones. It should be mentioned that production of free radicals occurs also in other organelles, e.g. in sarcoplasmic reticulum.

- relatively poor antioxidant defense systems in cardiac tissue. Cardiac cells contain relatively (compared to other tissues) low activities of the key antioxidant enzyme systems - SOD, catalase and GSH-peroxidase (GSH-Px) (48). Moreover, it has been experimentally demonstrated that chronic treatment with ADR in rats (cumulative dose 15 mg/kg i.p.) was accompanied with a decreased activity of selenium-dependent GSH-Px (10).

1.2 Free-radicals independent mechanisms

From the above-described data it may be concluded that free radicals play a pivotal role in the pathogenesis of ANT-induced cardiotoxicity. Several additional mechanisms have been proposed to be involved in the ANT cardiotoxicity. Briefly:

- histamine release (31,32)
- impairment of calcium homeostasis in the cardiac cells. This may result from:
 - a) Reduced accumulation of calcium by sarcoplasmic reticulum (19). This effect was observed in cultured rat myocardial cells incubated for 2 hr with 10 μM ADR. The used concentration, however, exceeded the maximal initial plasma concentrations ($\sim 5 \mu\text{M}$) after bolus administration of doses ranging between 15-90 mg/m² in patients (17). A decrease in mRNA expression for sarcoplasmic reticulum calcium transport proteins may underlie the described reduction in calcium sequestration in sarcoplasmic reticulum (4).
 - b) Inhibition of enzyme systems directly or indirectly regulating calcium movement (e.g. sarcolemmal Na^+/K^+ -ATPase, mitochondrial uptake of calcium) may play a role in „calcium overload“ of cardiac cells. This may result from the lipid peroxidation of the appropriate membranes (41). This effect was observed in isolated rat heart perfused by the Langendorff technique and exposed to ADR concentration of 86.2 μM . This concentration exceeded the achieved clinical concentrations many times (see preceding paragraph).
- interference with the autonomic control of the heart:
 - a) *Parasympathetic system.* DOX in concentrations of 0.01-3 μM (i.e. in the range of clinically relevant concentrations) acutely inhibited the negative chrono- and inotropic responses to the parasympathetic nerve stimulation of isolated dog atria due to the inhibition of acetylcholine release (28). This effect may contribute to the acute ANT cardiotoxicity characterized by various dysrhythmias.
 - b) *Sympathetic system.* In the chronic model of ANT cardiotoxicity in rabbits a decrease in both β_1 -adrenoceptors and noradrenaline content in cardiac ventricles was observed (43). In another experimental study the down-regulation of cardiac β_1 -adrenoceptors significantly correlated with heart failure (5).

2. Methods for detection and monitoring of anthracycline-induced cardiotoxicity

As mentioned previously the treatment with ANT is associated with several types of cardiotoxicity. During the early period of chemotherapy with ANT *acute manifestations* of ANT cardiotoxicity may occur: Non-specific ECG changes (e.g. a decreased QRS voltage, T-wave flattening, ST-segment elevation or depression, QT-interval prolongation) were detected by the continuous 24 hr ECG monitoring in 24-30% of patients. These changes were usually transient. However, more serious complications were also reported, e.g. myocardial infarction, LV dysfunction, severe hypotension, etc. (48).

The following text is primarily concerned with the methods for detection and monitoring of ANT-induced chronic cardiotoxicity. Early identification of patients at risk of development of chronic cardiomyopathy is fundamental because this enables to change the dosage schedule, evenly to stop treatment with ANT in time.

There are several methods currently used for the detection and monitoring of chronic ANT cardiotoxicity:

- ECG measurement
- Biochemical markers
- Determination of cardiac functional status
- Morphologic examination

2.1 ECG measurement

In 37 asymptomatic patients who received ANT (ADR and DAU in a total dose of 100-2030 mg/m²) ECG parameters showed no significant changes (57). On the other hand, in 20 asymptomatic women treated with high dose ANT chemotherapy an autonomic impairment was observed using heart rate variability analysis. This parameter was abnormal in most (85%) patients (59).

2.2 Biochemical markers

Natriuretic peptides. An increase in plasma concentrations of natriuretic peptides (atrial natriuretic peptide - ANP, brain natriuretic peptide - BNP) reflects neuroendocrine activation accompanying a decrease in LV function. Thirty adult patients with non-Hodgkin's lymphomas received DOX in a cumulative dose of 400-500 mg/m². There was a significant negative correlation between an increase in plasma ANP concentration and a decrease in LVEF. However, a decrease in LVEF started after the DOX cumulative dose of 200 mg/m², whereas an increase in ANP plasma concentrations was observed after the dose of 400 mg/m² (47). In another study with twenty seven patients receiving ANT persistent elevations in plasma BNP showed a poor prognosis in contrast to a transient increase. An increase in BNP levels correlated with diastolic dysfunction (58).

Cardiac troponin T (cTnT). In spontaneously hypertensive rats DOX in a cumulative dose of 7 mg/kg caused ele-

vations in serum cTnT concentrations with only minimal histological changes in cardiomyocytes (24). In our experimental study an elevation in cTnT preceded premature death in rabbits treated with DAU (1). The possible usefulness of cTnT as an early marker of ANT cardiotoxicity remains to be evaluated clinically.

2.3 Determination of cardiac functional status

Systolic function

Of the systolic function parameters the left ventricular ejection fraction (LVEF) is routinely used to detect ANT cardiotoxicity. This parameter is obtained by angiocardiology or by echocardiography (ECHO), the former being more accurate than the latter (14,40). Though indices of the systolic function (LVEF, mean velocity endocardial circumferential fibre shortening - V_{cfmean} , systolic time intervals) seem to precede the symptoms of chronic heart failure (CHF) in patients treated by ANT, they may not change significantly in asymptomatic patients with silent (yet reversible) myocardial damage (57). Exercise LVEF methods are sometimes used to determine if cardiac reserve is adequate for patients to tolerate additional chemotherapy (40).

Diastolic function

The results of several studies with ANT chemotherapy showed that the parameters of LV diastolic function could be more sensitive for detection of *early* asymptomatic myocardial damage than those of systolic function. In 37 patients treated with ANT (ADR or DAU in a cumulative dose of 100-2030 mg/m²) the indices of the rapid filling period (peak filling rate - PFR, normalized PFR) showed a significant decrease while ECG and systolic parameters did not change significantly (57). In 34 children receiving ANT chemotherapy (26-1100 mg/m²) conventional ECHO disclosed no difference as compared with normal control subjects. On the other hand, in ANT treated children normalized PFR was significantly lower and time to PFR was prolonged compared with the controls (20). In 22 asymptomatic patients (survivors of childhood cancer treated with ANT) the routinely used ECHO methods revealed no dysfunction. Dobutamine stress ECHO demonstrated the LV diastolic dysfunction as indicated by a decrease in mitral E/A ratio (the ratio of early to late peak filling velocity) (33). An alteration of diastolic function after ANT treatment may be due to myocardial oedema resulting from the membrane damage induced by lipid peroxidation (9).

2.4 Morphologic examination

Endomyocardial biopsy is highly effective for diagnosis of ANT cardiomyopathy, but due to invasiveness it is indicated only for selected patients (32). This examination can be replaced by a new non-invasive method using radioactive monoclonal antibodies against cardiac myosin (¹¹¹In-anti-myosin) (14).

3. Prophylaxis for anthracycline-induced cardiotoxicity

Multifactorial and incompletely understood pathogenesis of ANT cardiotoxicity partly explains a plenty of tested compounds and various other approaches in an effort to reduce this toxic effect. The prophylaxis can be partly achieved by:

- Cardioprotective agents
- Modification of dosage schedule
- Analogues of anthracyclines less toxic than doxorubicin or daunorubicin

3.1 Cardioprotective agents

A number of cardioprotective agents studied either experimentally or tested clinically can be subdivided into two groups according the proposed mechanisms of ANT cardiotoxicity that should be modified by administration of cardioprotectants.

Cardioprotective agents affecting free-radicals dependent mechanisms of ANT cardiotoxicity

Dexrazoxane (ICRF-187;ADR-529). A bisdioxopiperazine compound originally developed as an antitumour agent (11) is the *only* clinically approved drug for the prophylaxis of ANT cardiotoxicity in cancer patients (65). This compound has been found to be cardioprotective in all animal models of ANT cardiotoxicity, i.e. in rabbit, rat, mouse, miniature swine and dog (22,23,49). The protective effect appears to be due to either removal of iron from

ANT-iron complexes or binding free (or loosely bound) iron and subsequent reduction of free radicals production (21,53,65). At the same time response to anticancer chemotherapy and non-cardiac toxicities appears to be unaffected (67). However, administration of dexrazoxane at doses of 600-750 mg/m² (with a fixed dose of DOX 60 mg/m²) every three weeks resulted in neutropenia (26). Similarly, a trend toward increased haematologic toxicity was observed in pediatric sarcoma patients treated among others by DOX (50 mg/m²) and dexrazoxane (1000 mg/m²). Moreover, in this study a significantly higher incidence of transaminases elevations was observed (67). It can be stated that dexrazoxane provides effective protection against ANT cardiotoxicity. On the other hand, the toxic potential of this agent (especially hemato- and hepatotoxicities) encourages further investigation of new cardioprotectants with lower toxicity.

The table 1 illustrates some agents that have been experimentally studied for their possible cardioprotective activity.

It is evident that under specific conditions some tested compounds exhibited cardioprotective action. In interpretation of the achieved results one should take into account:

- concentrations used in some *in vitro* studies many fold exceeded clinical relevant levels of ANT
- protection by antioxidant enzymes could be scarcely expected in *in vivo* conditions
- protective action documented in acute models of ANT cardiotoxicity does not necessarily mean that similar action could be also seen in chronic models

Tab. 1: Some cardioprotective agents studied in animal models of ANT cardiotoxicity.

| <i>Agent</i> | <i>Model, dose, concentration</i> | <i>Notice</i> |
|--|--|---|
| L-carnitine | rat; DOX in a cumulative dose 15 mg/kg i.p. in 6 doses/12 wk | reduced lipid peroxidation (37) |
| glutamine | rat; DOX, single dose 9 mg/kg i.v. | maintenance of tissue GSH levels (7) |
| amifostine | rat; isolated perfused heart, DOX 25 µM | protection; coronary vasodilatation (44) |
| captopril | rat; ADR in a single dose 15 mg/kg i.v. | beneficial effect (2) |
| thymoquinone | mouse; DOX in a single dose 20 mg/kg i.p. | protection (3) |
| melatonin | rat; ADR in a cumulative dose 15 mg/kg | prevention of lipid peroxidation (42) |
| manganese dipyridoxyl diphosphate | mouse; isolated atria, DOX 120 µM | protection (chelating activity) (60) |
| deferoxamine | rat; culture of heart cells, DOX 1,7 µM | protection <i>only</i> in iron overloaded cells (25) |
| venoruton - standardized mixture of flavonoids | mouse; DOX in a cumulative dose 16 mg/kg i.v./4 wk | protection (iron chelation, scavenging activity) (61) |
| propolis (bee glue) | rat; DOX in a single dose of 10 mg/kg i.v. | protective effect due to flavonoids (29) |
| curcumin | rat; ADR in a single dose of 30 mg/kg i.p. | inhibition of lipid peroxidation (63) |
| vitamin E | rabbit; ADR in a cumulative dose of 40.8 mg/kg i.v. during 17 wk | only large doses showed partial protection (62) |
| superoxide dismutase | rat; perfused heart, ADR 1 nM | inhibition of OH [•] production (50) |
| catalase | rat; perfused heart, ADR 1 nM | complete abolition of OH [•] production (50) |
| selenium supplementation | rat; ADR in a cumulative dose of 15 mg/kg i.p. | decreased lipid peroxidation (10) |

- based on the results achieved primarily in chronic models of ANT cardiotoxicity, flavonoids, L-carnitine and iron chelators deserve further studies in order to make their possible protective role in chronic ANT cardiotoxicity more accurate

Cardioprotective agents affecting free-radicals independent mechanisms of ANT cardiotoxicity

Sodium cromoglycate inhibited histamine release from rat peritoneal cells *in vitro* induced by epirubicin and ameliorated both acute (20 mg/kg i.p.) and chronic (3x8 mg/kg i.p./3 wk) epirubicin cardiotoxicity (31).

Calcium channel blockers (nifedipine, flunarizine, verapamil) increased accumulation of ANT (DOX, DAU) in cultures of rat cardiomyocytes and thus potentiated cardiotoxicity (52). In 20 wk study verapamil significantly potentiated chronic cardiotoxicity of DOX in dogs (6).

Theophylline significantly inhibited the release of histamine induced by ADR in a concentration of 172 μ M from rat peritoneal cells *in vitro*. It also displayed both acute and chronic cardioprotection in mice against ADR cardiotoxicity (single dose of 15 mg/kg i.p., 3x5 mg i.p./15 days, resp.) (32).

3.2 Modification of dosage schedule

ANT are usually administered as a single dose infusion (over several minutes) every 3 wk (51). Other dosage regimens have been used in attempt to reduce cardiotoxicity. The results are, however, equivocal. E.g. a weekly dose schedule of DOX was reported to be associated with a significantly lower incidence of CHF (64). On the other hand, consecutive daily dose schedule (i.e. the same cumulative dose is administered for 3 consecutive days in one third doses) did not alter the incidence of DOX cardiotoxicity in children with malignancy (the follow up period 4-180 months) (12). Therefore, other dose schedules should be further investigated.

3.3 Analogues of anthracyclines less toxic than doxorubicin or daunorubicin

More than thirty years since the discovery of DAU and DOX thousands of ANT analogues have been synthesized to find compound with a higher effectiveness/toxicity ratio (56). Epirubicin (4'-epimer of DOX) was reported to be less cardiotoxic than DOX in equivalent low cumulative doses (9). In contrast, high dose schedules of epirubicin (150 mg/m² every 3 wk) in patients with soft-tissue sarcomas were not a preferred alternative to standard-dose DOX (75 mg/m²/3 wk). Moreover, epirubicin was more myelotoxic than DOX (45). It seems likely that none of ANT analogues has higher antitumour efficacy than two original compounds (66). At present DOX still remains the corner-stone of ANT group of antineoplastic agents.

Other way to decrease cardiotoxicity of ANT were the efforts to alter pharmacokinetics of original ANT. Liposomal encapsulation of DOX or DAU may reduce free drug plasma concentrations, increase distribution in tumours with subsequent increase in antitumour activity and reduction of toxicity, including the cardiac one (27). While a reduction of the cardiotoxicity of DOX or DAU was observed experimentally (49,68), no positive effects were demonstrated in patients with advanced breast cancer treated with liposome-encapsulated DOX (55). The authors of this clinical study stated that administration of high-dose liposome-encapsulated DOX (135 mg/m²/3 wk i.v. bolus) did not warrant further investigation.

5. Conclusions

During the last thirty years ANT have been among the most effective and widely used antineoplastic drugs. Their usefulness is, however, limited by a cumulative dose-related cardiotoxicity. The precise mechanisms of this adverse effect are not clear as yet. The pathogenesis seems to be multifactorial. It is likely that the principal role is exerted by free oxygen radicals generated by redox-cycling of ANT molecule (its quinone moiety) and/or by the formation of ANT-ferric ion complexes. The iron catalyzes the OH[•] (hydroxyl radical) production via Haber-Weiss reaction. The selective toxicity of ANT against cardiomyocytes results from high accumulation of ANT in cardiac tissue, appreciable production of oxygen radicals by mitochondria, which are abundant in cardiac cells, and relatively poor antioxidant defense systems.

Several additional mechanisms have been proposed to play a role in ANT cardiotoxicity, e.g. calcium overload, histamine release and impairment in autonomic regulation of heart function.

Early identification of ANT cardiotoxicity is fundamental for possible change in dosage schedule, evenly stopping the treatment with ANT. The currently used methods comprise ECG measurement, biochemical markers, functional measurement and morphologic examination.

For the prophylaxis of ANT cardiotoxicity different approaches have been tested. Among a plenty of studied compounds only dexrazoxane (ICRF-187) has been approved for clinical use. Its protective effect likely consists in intracellular chelating of free (or loosely bound) iron. However, dexrazoxane itself may cause myelotoxicity, esp. in high doses. This fact encourages for investigation of new cardioprotective agents with lower toxicity. Orally active iron chelators and flavonoids attract more attention. Modification of dosage schedule and synthesis of new ANT analogues, or new pharmaceutical formulation of the „classical“ ANT (i.e. DOX, or DAU), may represent alternative approaches to mitigate ANT cardiotoxicity while preserving antitumour activity.

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