Doxorubicin in experimental and clinical heart failure

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Summary

Doxorubicin-induced heart failure is a rare but serious illness due to the well-known treatment difficulties. Prevention strategies have not demonstrated the expected success and unfortunately, this specific type of heart failure does not respond to the usual medical therapy as other kinds of heart failure. Therefore, surgical procedures may be necessary in some patients. Cardiac transplantation is performed in most cases but it requires the cure of the neoplastic disease. This usually requires a recurrence-free interval of several years which is associated with a high attrition rate in these patients due to their cardiac disease. Therefore, other conservative and surgical treatment concepts were developed during the last years. This review presents the most common procedures and discusses their efficacy as well as their clinical applicability.

Keywords: End-stage heart failure; Doxorubicin; Cardiac surgery

1. Introduction

1.1. Incidence

Doxorubicin is a powerful drug in the fight against many kinds of cancer (for example, leukemias, lymphomas, breast and esophageal carcinomas, osteosarcomas, Kaposi's sarcoma, soft-tissue carcinomas, childhood tumors, testicular, gastric, and ovarian cancer, liver, bile-duct, pancreatic, and endometrial carcinomas, oat-cell carcinoma of the lung [1,2]). The most serious drawback of doxorubicin is its dose-dependent, obviously irreversible cardiotoxic effect [1]: The incidence of congestive heart failure is 4% in patients receiving 500–550 mg/m² and increases to 18% in patients receiving 551–600 mg/m² and to 36% in patients receiving >601 mg/m² [2]. In order to minimize this risk, an empirical dose limit of 500 mg/m² was suggested, but even in these patients cardiomyopathy developed in up to 1% [1,2]—in some patients even 4–20 years after the completion of chemotherapy [3]. Other authors have reported significantly higher percentages of heart failure patients (5%) at lower doses (400 mg/m² [4]). Beside the cumulative dose, older or very young age, a combination therapy, hypertension, liver disease, radiation of the left chest or mediastinum as well as preexisting cardiac disease seem to be added risk factors for doxorubicin-induced heart failure [1,2,4,5]. Furthermore, since the number of long-term survivors of cancer who have received doxorubicin increases continuously, these patients represent one of the largest and ever-increasing group of patients at risk from premature heart failure [6].

1.2. Cause

The exact causal mechanism of doxorubicin-induced cardiomyopathy remains unclear, but most of the evidence indicates that free radicals accompanied by a decrease of endogenous antioxidants and the subsequent increase in oxidants results in enhanced oxidative stress leading to a slow loss of myofibrils and vacuolization of myocardial cells which are the typical changes in the doxorubicin-induced heart failure [2]. Additional myocardial damage may be caused by an increase in tissue calcium, the inhibition of nucleic acid protein synthesis, lipid peroxidation, the release of vasoactive amines, TNF-α and interleukin-2, liberation of cytokine from the tumor, changes in adrenergic function, lysosomal alterations and the inhibition of the coenzyme Q10 and the sodium–potassium-activated ATPase [1,4,6].

1.3. Diagnosis

Each patient treated with doxorubicin should undergo an assessment of base-line cardiac function before chemotherapy, a regular monitoring during treatment and a close lifelong follow-up [2]. Neither the physical examination nor the electrocardiographic changes are specific for the doxorubicin-induced cardiomyopathy [2]. Therefore, a transthoracic echocardiography evaluating particularly the ejection fraction should be the basis of the lifelong screening examinations. Further advantages of the echocardiography
are its high sensitivity, noninvasive nature, easy practicability, and low costs [7]. The diagnostic test with the greatest specificity and sensitivity for doxorubicin-induced cardiomyopathy is the endomyocardial biopsy [8]. But beside its invasive nature it remains possible that patients with low-grade myocardial damage may develop severe congestive heart failure. Therefore, the endomyocardial biopsy should only be used with great caution as a guide for the continuation or termination of doxorubicin therapy or in patients with advanced heart failure [3,7].

1.4. Conservative management

Usually, traditional heart failure treatment (diuretics, digitalis, β-blockers, and ACE inhibitors) is performed but its effect is mostly very limited [5,9]. There are only a few publications reporting on an improvement of cardiac function after β-blocker therapy but these results must be examined further in well-designed, larger clinical trials [2,10]. Therefore, the most effective kind of treatment may be prevention of doxorubicin-induced cardiomyopathy without impairment of its antitumor benefits, but all approaches, such as use of doxorubicin analogues, limits of the overall doxorubicin dose, alternative drug delivery methods, and administration of doxorubicin in combination with cardioprotective agents, have had only a limited success [2,4,6,11,12]. According to Henderson and Frei [1], the solution of this problem may be the development of new semisynthetic doxorubicin analogues without cardiotoxicity or the concomitant administration of blocking agents.

Regarding this aspect, there is currently a great interest in matrix metalloproteinases (MMP) inhibition in the treatment of heart failure because MMP activation leads to a loss of myocardial collagens, myocyte slippage, ventricular dilatation, and progressive contractile dysfunction and eventually severe heart failure [13]. Since increased oxidative and nitrosative stress is implicated in the activation of MMPs and also in the cardiotoxicity of doxorubicin, MMP inhibition may diminish the degree of doxorubicin-induced heart failure [13]. Also, Pachter et al. [11] demonstrated in a similar animal model that prevention of doxorubicin-induced MMP activation resulted in improved cardiac function and survival. Furthermore, there is another important aspect in doxorubicin-treated patients: MMPs are known to contribute to degradation of interstitial collagens and the basal laminae leading to a more progressive primary tumor growth and a greater number and size of metastatic lesions [14,15]. And indeed, a correlation between tumor progression and clinical outcome on the one hand and MMP as well as tissue inhibitors of metalloproteinases (TIMP) levels on the other hand was reported [14]. Therefore, doxorubicin-treated patients with heart failure may benefit from a MMP inhibitor therapy in two ways: reduction of the degree of heart failure, and diminished tumor progress. But until now, this treatment option has not reached clinical applicability.

Therefore, it is generally recommended to stop the doxorubicin treatment when the first signs of heart failure are detected [1] and to start a conventional heart failure therapy. If this fails, surgical therapeutic options should be taken into consideration.

2. Surgical therapy

2.1. Experimental doxorubicin-induced heart failure models

Doxorubicin-induced heart failure models are currently still used in different experimental settings for research on therapeutical strategies for heart failure. The results of these trials may be helpful in the evaluation of the effectiveness of these strategies in the treatment of doxorubicin-induced heart failure. If research on surgical procedures is intended, large animal models are usually preferred due to size reasons [16].

Large animal doxorubicin-induced heart failure models are described in pigs and dogs. In 1979, van Vleet et al. [17] reported on the effects of intravenous doxorubicin administration in young pigs. They observed serious side effects (for example, diarrhea, weight loss, colitis, and bone marrow suppression) caused by the great doxorubicin doses necessary to produce a severe heart failure. Some animals even died due to these adverse effects. Therefore, this kind of administration cannot be recommended.

The other possibility for creation of a doxorubicin-induced heart failure model is the intracoronary doxorubicin administration in dogs. This allows application of markedly lower doxorubicin doses because of its direct effects on the myocardium without systemic adverse effects [18—20]. Two administration possibilities were described: administration via a catheter inserted in a retrograde fashion into the left main coronary artery using a diagonal branch of the left anterior descending coronary artery as access and connection of the catheter to a subcutaneous port [21,22] or via cardiac catheterization for each application [23]. Disadvantage of the last method is that the femoral artery has to be punctured under general anesthesia each week which becomes more and more difficult with increasing number of punctures. On the other hand, doxorubicin administration via a subcutaneously placed port is easily possible in sedated dogs. The resulting heart failure is dose-dependent [18] and histological as well as hemodynamic effects are similar to the doxorubicin-induced heart failure in human beings: Histological examinations showed interstitial fibrosis, cytoplasmic vacuolation, myocellular hypertrophy, and loss of contractile proteins [19—22]. Left ventricular diameters and volumes as well as left ventricular end-diastolic pressure increased, whereas fractional shortening, ejection fraction, stroke volume, and cardiac output decreased [19—23]. Furthermore, it was proven that doxorubicin produces a delayed cardiomyopathy leading to progressive lesions which becomes more severe even after discontinuation of doxorubicin administration [19,20,24,25]. In summary, results of surgical procedures in these animal models may be valuable for the treatment of patients with doxorubicin-induced heart failure.

2.2. Experimental surgical procedures

Cheng et al. [26,27] reported on the effects of dynamic cardiomyoplasty in the canine doxorubicin-induced heart failure model. Cardiomyoplasty with the left latissimus dorsi muscle was performed in ten dogs. Five died due to infection
or arrhythmias after the operation. After conditioning of the muscle they demonstrated a significant improved left and also right ventricular function when the muscle was stimulated and concluded that cardiomyoplasty improves indices of systolic and diastolic function in this canine model of chronic heart failure. Monnet and Orton [25] demonstrated in a similar trial that dynamic cardiomyoplasty reduced myocardial oxygen consumption but did not lower overall cardiac work.
Furthermore, this effect was also independent on skeletal muscle stimulation or not. Based on these two studies it seems questionable that dynamic cardiomyoplasty improves cardiac function in doxorubicin-induced heart failure. Since long-term results in human beings were also disappointing during the last 15 years, dynamic cardiomyoplasty was excluded from the international guidelines for heart failure management [28]. Therefore, it cannot be recommended for the treatment of doxorubicin-induced heart failure.

Some authors are of the opinion that the major beneficial effect of dynamic cardiomyoplasty is the prevention of progressive cardiac dilatation, the so-called girdling effect [29]. If this is true the same effect may be achieved by passive cardiomyoplasty. Shah et al. [30] and Vaynblat et al. [31] reported on a canine doxorubicin-induced heart failure model in which cardiac binding was performed with a Gore-Tex membrane directly after insertion of the intracoronal catheter for doxorubicin administration. They demonstrated a better survival and a less depressed cardiac function in the treatment group. The major drawback of this study is the placement of the membrane before heart failure development—this does not correspond to the clinical situation where patients are usually treated after heart failure development. In other experimental models (intracoronary microembolizations in dogs, rapid pacing in sheep) cardiac binding was performed after heart failure development [32,33]. Also in these settings the authors demonstrated an amelioration of left ventricular remodeling and an improvement of left ventricular function. Based on this premise, this surgical procedure has been performed in humans with dilated cardiomyopathy, in most cases with the Acorn® Cardiac Support Device [34—36]. Because short and mid-term results were promising worldwide, randomized trials are currently performed to examine the value of passive cardiomyoplasty in the treatment of dilated cardiomyopathy [37,38]. If this kind of surgical therapy also works in patients with doxorubicin-induced heart failure is not known until now because to our knowledge there are no reports on passive cardiomyoplasty in patients with doxorubicin-induced heart failure.

Partial left ventriculectomy was introduced by Batista et al. [39] in 1996. Since there was no suitable animal model for this kind of heart failure surgery, we developed a modified doxorubicin-induced canine heart failure model and were able to demonstrate that partial left ventriculectomy also improved left ventricular function in this very specific type of heart failure [19,20]. Another method for left ventricular volume reduction similar to partial left ventriculectomy was developed by Lunkenheimer et al. [40]: They used an aspirator cup for plication of the left ventricular lateral wall in healthy pigs. The aspirated segment (usually the inter-papillary segment) was fixed by splints and sutures below the aspirator cup. This resulted in a reduction of the left ventricular volume similar to that achieved after excision of the left ventricular lateral wall in partial left ventriculectomy. Ideally, the aspiration procedure can be performed without cardiopulmonary bypass and cardioplegic cardiac arrest (in contrast to partial left ventriculectomy) thus reducing the surgical invasiveness markedly. Therefore, partial left ventriculectomy (or its modifications) may be taken into consideration as an alternative therapeutic option in doxorubicin-treated patients who are not candidates for other treatment modalities [41]. To our knowledge, there are no reports on partial left ventriculectomy (or its modifications) in patients with doxorubicin-induced heart failure in the scientific literature. Results of partial left ventriculectomy in patients with other cardiac diseases, mainly dilated and ischemic cardiomyopathy, are contradictory. Therefore, presently partial left ventriculectomy cannot be evaluated conclusively [29].

Cell transplantation is a new, promising therapy for treating end-stage heart failure that has also been applied in doxorubicin-induced heart failure models [42,43]. Ishida et al. [42] reported beneficial effects of bone marrow mononuclear cell transplantation by direct injection into the left ventricular free wall and Suzuki et al. [43] demonstrated improved cardiac function after intracoronary skeletal myoblast infusion. Despite these promising results, cell transplantation remains associated with many unanswered questions such as the optimum number of transplanted cells, the number of surviving and differentiating cells, necessity of immunosuppression, the optimum route of application, the best kind of cells, the arrhythmogenic and neoaplastic potential of transplanted cells, and the most appropriate time of application. Furthermore, the working mechanism of transplanted cells is still unclear [43]. Various explanations include (1) improved contractile properties due to transplanted cells, (2) attenuation of adverse remodeling by secretion of endocrine or paracrine factors by grafted cells, (3) improved angiogenesis, (4) enhanced contractility of native cardiomyocytes, and (5) changes of the viscoelastic properties of the myocardial wall [43,44]. In summary, the effects of cell transplantation warrant more precise examinations before this kind of heart failure therapy can be recommended for human beings.

2.3. Clinical surgical procedures

Currently, the only treatment option that has been recognized as successful in doxorubicin-induced end-stage heart failure is cardiac transplantation [45—47]. In a small series of pediatric patients 1-, 2-, and 5-year survival rates of 100%, 92%, and 60%, respectively, were reported with a low risk of cancer recurrence [47]. But usually the proof that the neoplasm has been cured or a 5-year (some authors also accept shorter intervals in specific cases) cancer-free period is requested before transplantation [47—49]. Besides all other well-known drawbacks of cardiac transplantation including risk of infectious diseases and rejection, graft failure after 15—20 years (especially important in younger tumor patients), lifelong immunosuppressive therapy and follow-up, the long waiting time following chemotherapy results in a considerable number of patients who are at risk to die of cardiac failure. Mortality rates up to 70% [50] have been reported. Based on these considerations, other treatment strategies need to be developed.

Implantation of ventricular assist devices has been proven to be effective in patients with end-stage heart failure [51]. This option also has been used in some patients with postchemotherapy heart failure [48,50]. One patient with cardiogenic shock and a life expectancy less than 6 months due to metastatic leiomyosarcoma underwent implantation of a biventricular assist device as life-saving therapy. Due to
ongoing bleeding complications the patient was weaned from the device because the echocardiographic studies revealed an improved cardiac function. Unfortunately, this patient died a few days later [50]. Another patient was supported for 1512 days with a Novacor LVAD due to a cardiogenic shock after chemotherapy for Castleman disease. During this time he developed several episodes of driveline infections, one episode of cerebral embolism and a moderate incompetence of the Novacor inflow valve. After this 4-year period without any neoplastic recurrences this patient underwent cardiac transplantation because repeated weaning trials were unsuccessful [48]. Both cases illustrate the complete dilemma with assist devices in patients with postchemotherapy heart failure: Device implantation may be the only lifesaving treatment option in these patients. But if these patients cannot be bridged to recovery, they must be supported for years until the neoplastic disease is cured to undergo cardiac transplantation. During this time they have a great risk of infectious, thromboembolic and bleeding complications as well as technical failures [48,50—53]. A different alternative in these patients may be the implantation of assist devices as destination therapy [54—56] which would help to avoid the dilemma of cardiac transplantation in tumor patients. On the one hand, results of long-term support in LVAD patients have improved over time, but on the other hand the rate of complications as well as costs remain considerable [51,54,55] (Fig. 1; Table 1).

3. Conclusions

Doxorubicin-induced heart failure is rare but associated with a poor prognosis. Patients treated with doxorubicin should undergo a lifelong screening for doxorubicin-induced heart failure based on a thorough echocardiographic examination. An endomyocardial biopsy should only be used as a guide for the continuation or termination of doxorubicin therapy in patients with advanced heart failure or patients with a delayed development of heart failure after doxorubicin treatment. If a doxorubicin-induced cardiomyopathy is diagnosed a conservative treatment should be tried, especially with ß-blockers. In therapy-refractory patients who suffer from an advanced heart failure, surgical treatment options such as cardiac transplantation and ventricular assist device implantation should be taken into consideration but these procedures are associated with high costs, a considerable perioperative risk, and serious ethical problems. Unfortunately, alternative surgical options such as dynamic and passive cardiomyoplasty, partial left ventriculotomy, and cell transplantation have not been proven as effective clinical therapies until now. Therefore, since these therapeutic options in advanced doxorubicin-induced cardiomyopathy are disappointing, new treatment protocols or prevention strategies, such as MMP inhibitors, seem to be the most promising concepts to lower the risk of doxorubicin-induced heart failure.

References


