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Review

A review of the preclinical development of dexrazoxane

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ABSTRACT

We review here the experiments by which dexrazoxane was identified as a protectant against two serious anthracycline toxicities: cardiotoxicity and accidental extravasation injury. These experiments led to the successful use of dexrazoxane as a cardioprotectant in clinical cancer trials. Several preclinical studies established that dexrazoxane reduced cardiotoxicity without altering the anti-neoplastic activity of doxorubicin and its analogs and without increasing non-cardiac tissue toxicity. In animal models, dexrazoxane has also reduced the toxicity of several other substances, including alloxan, acetaminophen, bleomycin, and oxygen. Experimental models have further led to the use of serum biomarkers to detect and monitor subclinical cardiotoxicity in children and adults with cancer. Studies of the chemistry, biochemistry, metabolism, pharmacokinetics and pharmacodynamics of dexrazoxane have so far revealed two important cytoprotective activities: it is rapidly metabolized to an active iron chelation form (ADR-925), which prevents oxidative stress on cardiac tissue, and it may be cytoprotective by inhibiting topoisomerase IIβ. The animal models described here suggest a potential clinical use for dexrazoxane in reducing anthracycline-mediated cardiotoxicity when given before each anthracycline dose and in preventing accidental anthracycline extravasation. Dexrazoxane is currently licensed to treat these two serious conditions.

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1. Introduction

Much effort has been spent searching for ways or drugs to eliminate the acute and long-term cardiotoxicity of anthracyclines without reducing their impressive antitumor efficacy or creating new toxicities. Extensive experiments in six animal species, supported by elegant collateral biochemical and pharmacological studies, have established dexrazoxane as the most promising drug to date to meet these goals. Data from mouse models also established dexrazoxane as the antidote of choice for treating accidental anthracycline extravasation. Here, we summarize the large body of in vivo and in vitro preclinical experiments that identified the characteristics of anthracycline cardiotoxicity and the best clinical strategies for administrating dexrazoxane to prevent myocyte damage.

2. Experimental Rationale for Dexrazoxane Protection Against Anthracycline Cardiotoxicity

The anthracyclines doxorubicin and daunorubicin were introduced as antineoplastic agents 40 years ago [1]. These agents exert a broad spectrum of antitumor activity, and as a result, were rapidly incorporated into treatment for both hematologic and solid tumors. Anthracyclines remain important in cancer chemotherapy. However, cardiotoxicity is a major dose-limiting effect of these agents [2], although their clinical cardiotoxic effects were not initially detected in preclinical studies.

Studies investigating the possibility that certain substances might exert cardioprotective actions could only begin once clinical aspects of doxorubicin cardiotoxicity were reproduced in appropriate animal models [3–6]. The clinical symptoms associated with doxorubicin cardiotoxicity reported in early chemotherapy studies consisted of hypotension, tachycardia with or without arrhythmia, and congestive heart failure [7]. Subsequently, experiments were designed to determine whether any of these types of cardiac changes could be duplicated in animal models. An early study in Syrian Golden Hamsters and Rhesus Monkeys found that high doses of daunorubicin caused acute ventricular arrhythmias [8–10]. These studies identified several adrenergic blocking agents that could either prevent arrhythmias or increase the arrhythmic-causing dose of daunorubicin. These observations indicated that acute cardiac toxicity might in part be mediated by a component of the sympathetic nervous system [10].

3. Isolated Heart Experiments and In Vivo Animal Models

The isolated perfused dog heart was used as a model to determine whether doxorubicin exerted direct effects on the myocardium (as indicated by electrocardiographic characteristics, heart rate, coronary perfusion pressure, and left ventricular force of contraction) [11]. Both

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doxorubicin and daunorubicin consistently and markedly increased coronary perfusion pressure, indicating increased vascular resistance. Agents that prevented or reduced daunorubicin-induced arrhythmias in hamsters and rhesus monkeys did not reduce the increases in perfusion pressure [12]. Eventually, ethylenediaminetetraacetic acid (EDTA) was discovered to negate or reduce the increases in perfusion pressure when administered before doxorubicin or daunorubicin. At that time, two EDTA-related bisdioxopiperazine compounds from the Imperial Cancer Research Fund (ICRF-159 'razoxane' and ICRF-187 'dexrazoxane') were being evaluated by the National Cancer Institute for antitumor activity. Surprisingly, pretreatment of the isolated heart model with either razoxane or dexrazoxane blocked doxorubicin-induced increases in coronary perfusion pressure [12].

The information from the isolated heart experiments was the basis for additional studies in the Syrian Golden Hamster. This model, again, consisted of administering single, high-intravenous doses of daunorubicin [13]. In these studies, the animals were pretreated with a single intraperitoneal dose of razoxane or dexrazoxane 30 min before daunorubicin administration. Exposure to either razoxane or dexrazoxane markedly increased survival and decreased overt toxicity when compared to those animals receiving only daunorubicin. The pretreated animals had less-severe cardiac lesions than did those receiving only daunorubicin. Changes in the heart and non-cardiac tissues, such as the kidney and liver, did not appear to be responsible for the high number of deaths on day 5 after daunorubicin administration. However, the gastrointestinal tract was severely altered in the animals given only daunorubicin, however, these alterations were much less severe in animals given razoxane or dexrazoxane before daunorubicin [13].

The attenuation of acute, high-dose daunorubicin lethality and toxicity was the first in vivo indication that razoxane and dexrazoxane could be cardioprotective [13]. However, the relevance of this effect was still not clear because the dose-limiting cardiac changes occur when low doses of anthracycline are administered over long periods.

The first attempt to reproduce a more clinically relevant animal model of anthracycline cardiotoxicity was in rabbits given daunorubicin (rabbits were unable to tolerate similar doses of doxorubicin) at 3-week intervals, with or without dexrazoxane (dexrazoxane was used exclusively in long-term studies because of its increased water solubility) over 15 weeks [14]. After 15 weeks, myocardial changes in rabbits were similar to those in the hearts of anthracycline-treated patients. Cardiac lesions were found in all animals given only daunorubicin. In contrast, myocardial changes were either absent or markedly less severe in rabbits given dexrazoxane before daunorubicin. This finding was the first indication that dexrazoxane could be cardioprotective during long-term daunorubicin administration and that this cardioprotective activity continued at least too shortly after the final dose of daunorubicin was administered [14].

The persistence of dexrazoxane cardioprotection was studied in rabbits, who received 3.2 mg/kg daunorubicin, with or without 25 mg/kg dexrazoxane, once every 3 weeks for six treatment periods [15]. At examination 3 months after the last treatment period, all seven rabbits given only daunorubicin had myocardial lesions of varying severity. In contrast, the hearts from five of seven animals given dexrazoxane before daunorubicin appeared to be normal, and the hearts of the other two animals had only minimal myocardial lesions. These results documented that dexrazoxane could provide prolonged protection against daunorubicin-induced cardiomyopathy rather than only delaying the onset of cardiomyopathy [15].

Toleration issues limited studies in rabbits to daunorubicin. Whether dexrazoxane would also reduce doxorubicin cardiotoxicity was next pursued in beagle dogs [16]. These animals were treated weekly with 1 mg/kg doxorubicin for 15 weeks (cumulative dose, 15 mg/kg) or 1.75 mg/kg doxorubicin every 3 weeks (14.4 mg/kg) either alone or 30 min after pretreatment with dexrazoxane 12.5 mg/kg. In each study, both the incidence and severity of the myocardial changes were reduced in dogs given dexrazoxane prior to doxorubicin.

In yet another animal model [17], long-term, weekly treatment with 1 mg/kg doxorubicin (cumulative dose, 12 mg/kg) caused severe myocardial and renal lesions in male spontaneously hypertensive rats and genetically related Wistar-Kyoto. The cardiac lesions were more severe in the spontaneously hypertensive rats (confirming clinical observations that hypertensive patients are more sensitive to doxorubicin). Another study also noted that pretreatment with dexrazoxane significantly reduced the severity of the cardiac lesions in both strains of rats [18].

The studies described above used a fixed dexrazoxane pretreatment time of 30 min [14,16,18]. It was important to determine whether pretreatment time affected cardioprotectant activity. Beagle dogs were treated either with 1.75 mg/kg doxorubicin (cumulative dose, 14.0 mg/kg) alone or dexrazoxane (35 mg/kg) given 30 min before, simultaneously with or 2 h after doxorubicin every 3 weeks [19]. After seven treatment periods, dogs receiving dexrazoxane at any time had significantly less-severe myocardial lesions than dogs receiving doxorubicin alone. Cardioprotection was more pronounced when dexrazoxane was given 30 min before or simultaneously with doxorubicin than when it was given 2 h after doxorubicin. These studies indicated that the timing of the dexrazoxane administration in relation to doxorubicin can affect the degree of cardioprotection [19].

Another important question was whether dexrazoxane actually influenced the ability to tolerate a greater cumulative dose of doxorubicin. Beagle dogs were treated at 3-to-4 week intervals with doxorubicin (1.75 mg/kg), either alone or 15 min after dexrazoxane (25 mg/kg). The eight dogs treated with doxorubicin alone tolerated only seven to eight doses (cumulative doses of 12.25–14.0 mg/kg) and had severe myocardial lesions. Both the incidence and severity of cardiac changes were significantly reduced in dogs given dexrazoxane before doxorubicin. Of the five dogs dosed 20 to 25 times with doxorubicin (cumulative dose, 35 to 43.75 mg/kg), four had no observable lesions, and one had minimal myocardial changes. Of three dogs able to tolerate a cumulative dose of 52.0 mg/kg (30 doses), one had mild lesions and two had moderately severity lesions. This study clearly showed that dexrazoxane provided substantial cardioprotection, which made it possible to tolerate potentially lethal cumulative doses of doxorubicin [20].

These and numerous other studies encouraged the examination of dexrazoxane as a protectant against the cardiotoxic effects of doxorubicin in humans. The first clinical evaluation of dexrazoxane (in women receiving doxorubicin for breast cancer [21]) confirmed its cardioprotective activity and showed that it did not increase non-cardiac toxicity nor reduce the anti-neoplastic activity of doxorubicin. Dexrazoxane has also reduced the long-term myocardial consequences of children treated with doxorubicin [22]. Currently, dexrazoxane is the only drug approved to reduce doxorubicin cardiotoxicity in humans [23]. However, its use has been limited to adults with metastatic breast cancer who would benefit from additional doxorubicin treatment but in whom the cumulative dose of doxorubicin is already above 300 mg/m^2.

Preclinical models have been useful in reproducing the clinical characteristics of anthracycline cardiotoxicity and in identifying a potentially useful cardioprotectant, dexrazoxane. Clinically, it is also important to detect the onset and progression of anthracycline-induced cardiomyopathy. Conventional methods for monitoring heart function, such as echocardiography, radionuclide ventriculography and cardiac magnetic resonance, detect changes only after a certain degree of damage has already occurred. Preclinical models have again proved useful in testing serum biomarkers for detecting anthracycline-induced myocardial injury. Serum concentrations of cardiac troponin T were elevated in spontaneously hypertensive rats after treatment with cumulative doses of 7 and 12 mg/kg doxorubicin [24]. A more detailed study of cumulative doses ranging from 2 to 12 mg/kg also showed excellent correlations between the total cumulative dose of doxorubicin, the severity or cardiac injury and increases in serum cardiac troponin T concentrations [25].