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Paola Della Torre · Anthony R. Imondi
Claudio Bernardi · Arturo Podestà
Donatella Moneta · Mariagrazia Riflettuto
Guy Mazué

Cardioprotection by dexrazoxane in rats treated with doxorubicin and paclitaxel

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Abstract *Purpose*: Results of several clinical studies suggest that the combination of doxorubicin (DOX) and paclitaxel (PTX) is highly active against solid tumors. Both drugs are known to cause adverse cardiac effects, cardiomyopathy in the case of DOX and acute changes in cardiac rhythm in the case of PTX. It has been suggested that the addition of dexrazoxane (DZR) to this regimen may reduce the risk of cardiotoxicity. A model of chronic cardiomyopathy in the rat was used to determine whether DZR was tolerated and cardioprotective in a DOX + PTX combination. *Methods*: Male rats were treated once weekly for 7 weeks with one of the following vehicle and/or drug sequences: Group A, *M*/6 sodium lactate/saline/Cremophor EL (CEL); Group B, lactate/DOX/CEL; Group C, DZR/DOX/CEL; Group D, lactate/DOX/PTX; and Group E, DZR/DOX/PTX. DZR and DOX or their respective vehicles were given i.v. whilst PTX or CEL were given i.p. DZR, DOX and PTX were administered at 16 mg/kg, 0.8 mg/kg and 2.4 mg/kg, respectively, doses which caused minimal noncardiac toxicities. The hearts were examined histologically 5 weeks following the last treatment. *Results*: There were no deaths and no signs of overt toxicity during the 12 weeks of study. There was a significant decrease ($P < 0.01$) in white blood cell count in rats treated with DZR + DOX, DOX + PTX or DZR + DOX + PTX but not in those given DOX alone. Liver and kidney weights were increased in rats given DOX ($P < 0.05$) but not in those given DZR + DOX. PTX had no effect on the DOX-induced liver and kidney changes and did not interfere with the protective effect of DZR on the kidney. The severity and extent of cardiomyopathy expressed as the mean total score (MTS) for each treatment group, was similar for DOX and DOX + PTX (4.6 and 4.2, respectively). DZR provided significant cardioprotection ($P < 0.01$) when added to either DOX (MTS 2.0) or to DOX + PTX (MTS 2.1). *Conclusions*: The results suggest that PTX does not exacerbate the chronic cardiomyopathy caused by DOX and when added to the DOX + PTX combination, DZR retains its protective activity against DOX-induced cardiotoxicity without increasing noncardiac toxicity.

Key words Dexrazoxane · Doxorubicin · Paclitaxel · Cardiotoxicity

P. Della Torre · C. Bernardi · A. Podestà ·
D. Moneta · M. Riflettuto · G. Mazué
Worldwide Toxicology, Pharmacia & Upjohn,
20014 Nerviano (MI), Italy

A.R. Imondi (✉)
Battelle Memorial Institute, 505 King Avenue, Columbus,
Ohio 43201-2693, USA
Tel.: +1-614-424-7131; Fax +1-614-424-3716

Introduction

Doxorubicin (DOX) and paclitaxel (PTX) are among the most active drugs for the treatment of solid tumors. Results of several clinical studies suggest that these drugs are highly active when given in combination for the treatment of breast cancer [1, 8, 12, 19, 33]. There have also been encouraging results with DOX plus PTX in small-cell [34] and non-small-cell lung cancer [6]. Unfortunately, there was also an increase in the incidence of cardiotoxicity and congestive heart failure with this regimen in the initial clinical trials [8, 12]. In later trials, the incidence of cardiotoxicity was reduced by limiting DOX to six cycles and a cumulative dose of ≤360 mg/m^2 [11, 14]. Nevertheless, the potential for cardiotoxicity with the combination of DOX plus PTX is still of concern, especially for those patients who are at higher risk because of pre-existing heart disease, prior mediastinal radiotherapy or age [42]. Thus, additional approaches to lowering the risk of cardiotoxicity with this promising drug combination, such as extending the interval between administration of the DOX and the PTX [2] and substituting the less cardiotoxic anthracycline, epirubicin, for DOX [6], are being considered. The inclusion of a cardioprotective agent such as dexrazoxane (DZR) in the regimen has also been suggested [20, 35].

The efficacy of DZR has been demonstrated in many animal models of anthracycline-induced cardiotoxicity [16, 21] and in patients receiving DOX for the treatment of breast cancer [36, 38, 39], but there is little information regarding its safety and efficacy in the presence of PTX. Sparano et al. [35] conducted a phase I trial with DOX plus DZR with escalating doses of PTX in 15 patients with advanced breast cancer. No cardiotoxicity was seen in this study with cumulative doses of DOX of up to 600 mg/m^2 but this study was not designed to determine whether DZR was cardioprotective in this regimen. We conducted a study to determine the cardioprotective effects of DZR in rats treated chronically with either DOX alone or DOX plus PTX. Since the major focus of this study was the effect of the drug combinations on the development of cardiomyopathy over a period of 12 weeks, we selected doses of the drugs which would not cause significant noncardiac toxicities or affect survival of the rats during the study.

Materials and methods

Chemicals

DZR and DOX were manufactured by Pharmacia (now Pharmacia and Upjohn, Milan, Italy). DZR was provided as the lyophilized HCl salt and was reconstituted in *M*/6 sodium lactate. DOX was provided as the Adriablastin PFS formulation. PTX, supplied by Indena S.p.A., Milan, Italy, as a powder, was dissolved in Cremophor EL (CEL)/absolute ethyl alcohol (1:1) and then in a ratio of 1:9 with Sodium Chloride Injection.

Animals and experimental design

All animal experimentation was conducted in strict compliance with EU and Italian Guidelines for Laboratory Animal Welfare. Sprague Dawley [Crl:CD(SD)BR] male rats were obtained from Charles River, Italy. Only males were used since they are more sensitive than female rats to anthracycline-induced cardiac and noncardiac toxicities [21]. They were housed in pairs in cages with sawdust bedding in a room with controlled temperature (21 ± 1.5 °C) and humidity (55 ± 15%) and a 12-h light-dark schedule. They were allowed free access to water and 4RF21GLP pelleted food supplied by Mucedola S. r. l. (Milan, Italy). At the time of the first treatment, the rats were 7 weeks old and weighed 213 to 252 g.

The rats were assigned randomly (ten rats per group) to one of five groups with the following dosing sequence: group A, lactate/saline/CEL; group B, lactate/0.8 mg/kg DOX/CEL; group C, 16 mg/kg DZR/0.8 mg/kg DOX/CEL; group D, lactate/0.8 mg/kg DOX/2.4 mg/kg PTX, and group E, 16 mg/kg DZR/0.8 mg/kg DOX/2.4 mg/kg PTX. DZR or lactate were administered 30 min before the DOX or the saline. PTX or CEL were given immediately after the DOX or the saline. DZR and DOX, or their respective vehicles, were given by slow i.v. injection into a tail vein, whilst PTX or CEL were given i.p. The treatments were administered once weekly for 7 consecutive weeks. The rats were killed 5 weeks after the last treatment by exsanguination from the abdominal aorta, under complete i.p. sodium thiopental anesthesia.

Investigations

Mortality, general condition and individual body weights were recorded throughout the study. Blood samples were collected from five rats per group for hematology and clinical chemistry on days 21 and 42, prior to the third and seventh treatments, and at the end of the observation period (day 84). Post mortem examination included necropsies and weighing of the heart, kidneys and liver. The heart was quickly removed and fixed in 4% paraformaldehyde, dehydrated in ethanol, infiltrated and embedded in methacrylate. Sections (1 μm) were examined microscopically after staining with alkaline toluidine blue. The histopathological evaluation of the hearts was performed using the scoring system described by Solcia et al. [32], in which cardiomyopathy is expressed as a product of the severity and the extent of the damage. Severity (S) was defined as: grade 1, sarcoplasmic microvacuolations and/or inclusions, cellular edema, or interstitial edema; grade 2, as in grade 1 plus sarcoplasmic macrovacuolations or atrophy, necrosis, fibrosis, endocardial lesions and thrombi. Extent (E) was defined as: grade 0.5, less than 10 altered myocytes; grade 1, single altered myocytes; grade 2, scattered small groups of altered myocytes; grade 3, several small groups of altered myocytes; grade 4, groups of altered and confluent myocytes; and grade 5, most myocytes affected. The mean total score (MTS) for each group is $\sum$ (S × E)/number of animals.

Statistical analyses

Mean body weight and clinical chemistry data were analyzed by Bartlett's test for homogeneity of variance, Fisher's and Dunnett's tests for homogeneous data and the Cochran and Cox test for nonhomogeneous data. Hematology data and mean relative organ weights were analyzed by Duncan's Multiple Range test [37]. The MTS of the treated groups were compared to the control MTS using the Kruskal-Wallis test [25] followed by the Dunn one-tailed multiple comparison test [9]. The Wilcoxon test was used for comparing the MTS between treatment groups.

Results

Toxicity

There was no mortality or signs of systemic toxicity in any of the groups at any time during the study. There were no treatment-related effects on body weight. The only significant hematologic effect was in the number of leukocytes, due primarily to a decrease in the number of lymphocytes. The mean WBC on day 21, a week after the second treatment, was decreased significantly ($P < 0.01$) in the rats which received DOX with either DZR, PTX or both (Table 1). The mean WBC in these groups were also lower than in the control and DOX alone groups on day 42 but the differences were not statistically significant. By day 84, the WBC in all groups were essentially the same.

There were slight but nonsignificant increases in serum lipids (triglycerides, cholesterol and phospholipids) at the end of the study in the rats given DOX alone or DOX plus PTX (data not shown). There was an increase in the relative liver weight ($P < 0.05$) in rats given DOX, either alone or with either PTX or DZR + PTX (Table 1). DZR prevented the increase in liver weight in rats given DOX alone. Relative kidney weights were also increased with DOX alone ($P < 0.01$) and in combination with PTX ($P < 0.05$), but these increases were blocked by DZR (Table 1). The increase in kidney weights with DOX alone and with DOX + PTX was

Table 1 Effect of paclitaxel on white blood cell count, liver and kidney weights, and cardiotoxicity in rats treated with doxorubicin and dexrazoxane

Group	Treatment[a]	WBC[b]	Relative weight[c]		Cardiotoxicity[d]
			Liver	Kidney	
A	Control	12.7 ± 3.8x	2.40 ± 0.24	0.62 ± 0.04	0
B	DOX	9.1 ± 3.1	2.93 ± 0.39^{*1}	0.75 ± 0.10^{*2}	4.6^{*2}
C	DZR + DOX	7.4 ± 1.8^{*2}	2.52 ± 0.17^{*3}	0.64 ± 0.03^{*3}	2.0^{*1,*4}
D	DOX + PTX	6.3 ± 0.8^{*2}	2.72 ± 0.30^{*1}	0.74 ± 0.07^{*1}	4.2^{*2}
E	DZR + DOX + PTX	6.4 ± 1.3^{*2}	2.71 ± 0.19^{*1}	0.66 ± 0.32^{*1,*3}	2.1^{*1,*4,*5}

$^{*1}P < 0.05$, $^{*2}P < 0.01$ vs group A; $^{*3}P < 0.05$, $^{*4}P < 0.01$ vs group B; $^{*5}P < 0.05$ vs group D
[a] DOX (doxorubicin) 0.8 mg/kg i.v. weekly for weeks 1–7; DZR (dexrazoxane) 16 mg/kg i.v. 30 min before DOX; PTX (paclitaxel) 2.4 mg/kg i.p. immediately after DOX
[b] White blood cells on day 21 ($\times 10^3/mm^3$). Mean ± SD, $n = 5$
[c] Organ weights as percentage of final body weight. Mean ± SD, $n = 10$
[d] Mean total score ± SD, $n = 10$

associated with moderate proteinuria (data not shown). Testes were not weighed but they were atrophic in all drug-treated groups.

Cardiotoxicity

Cardiomyopathic changes were present in the hearts of all rats given DOX, the MTS in each group being significantly greater than in the controls (Table 1). Qualitatively, the cardiac lesions in the DOX-treated groups were similar, consisting mainly of a multifocal vacuolar degeneration of the myocytes (sarcoplasmic micro- and macrovacuolations) and were given a severity score of 2. The most extensive cardiomyopathy was present in those rats given either DOX alone or DOX + PTX in which the extent of injury ranged from 1 to 4. The MTS in these groups were similar (4.6 and 4.2, respectively). DZR lessened the cardiotoxicity in rats given DOX alone (MTS 2.0, $P < 0.01$), as well as in those given DOX + PTX (MTS 2.1, $P < 0.01$). The extent of cardiomyopathy in the two groups given DZR ranged from 0.5 to 2.

Discussion

The cardiac effects of DOX, observed in several animal species and humans, are well-known and include both acute ECG perturbations and chronic progressive cardiomyopathy which may lead to congestive heart failure and death [26].

PTX also causes acute effects on the heart such as asymptomatic bradycardia, bradyarrhythmia and ventricular tachycardia in patients [31]; in newborn rat cardiac cells in vitro, it causes a decrease in the beating frequency and an increase in the number of arrhythmias [4]. Pouna et al. [29], using an ex vivo rat model, found that cardiac performance is not affected when rats are treated with PTX alone; however, when combined with DOX, PTX potentiates the decrease in cardiac contractility and relaxation capacity caused by DOX.

Chronic cardiomyopathy characteristic of anthracycline therapy has not been reported in either animals [23, 24] or humans [31] following PTX treatment. However, there are no reports of studies conducted to determine whether PTX would exacerbate the chronic cardiotoxic effects of anthracyclines in animals, and such studies would not be possible in humans.

In the initial clinical trials, the combination of DOX and PTX caused an increase in the incidence of cardiotoxicity [8, 12] as well as severe neutropenia and mucositis [12]. These effects were attributed to interference with the elimination of DOX and doxorubicinol from the body by PTX [13] and were minimized by giving the DOX several hours before the PTX [18]. The present study was intended to evaluate the chronic cardiotoxicity of DOX and its protection by DZR in the presence of PTX. The acute pharmacokinetic interactions between DOX and PTX were avoided by administering the PTX i.p. Although uptake of PTX into the systemic circulation from the peritoneal cavity is prolonged in humans [10] and mice [22], high and sustained levels of PTX are attained in extraperitoneal tissues following i.p. administration [22]. Since weekly administration of 8 mg/kg PTX by the i.p. route for 5 weeks has been shown to cause peripheral neuropathy in the rat [5], we chose a dose of 2.4 mg/kg weekly for the 7 weeks of treatment which caused a decrease in WBC when combined with DOX.

The present study demonstrated that PTX did not affect the severity or the extent of DOX-induced cardiomyopathy in the rat. Also, PTX did not interfere with the ability of DZR to ameliorate the cardiotoxicity caused by DOX. The dose of DOX selected for this study resulted in an MTS of 4.6, which is a submaximal cardiotoxic effect. For example, the MTS obtained with a dose of 1 mg/kg DOX once weekly for 7 weeks was 6.5, 5 weeks after the last treatment [7]. Thus, had PTX exacerbated the cardiotoxicity induced by DOX, it is likely that it would have been detected.

The effects of DOX on organs other than the heart were minimal. The DOX-induced renal and liver toxicity, which have been described by others [3, 27], and is

marked by an increase in the weight of these organs, does not occur in humans [27]. As shown previously, DZR prevented the effects of DOX on these organs [7, 17]. PTX did not exacerbate the effect of DOX on either the kidney or the liver and did not interfere with the protective effect of DZR on the kidney. The decrease in the number of WBC observed with DOX + DZR has been observed in earlier studies in the rat [7] and in humans [38]. Likewise, the combination of PTX + DOX caused a decrease in WBC count in the rat as has been reported in patients [8]. However, there was no additional myelosuppression in the rat when the three drugs were combined.

These results indicate that DZR maintains its cardioprotective properties without adding to the toxicity of a DOX + PTX combination and suggest that this three-drug combination may be useful clinically. However, the potential for DZR to interfere with the antitumor efficacy of PTX is not known. DZR is thought to exert its cardioprotective effect by chelating iron and blocking the generation of toxic free radicals [15]; however, it is also an inhibitor of topoisomerase II [40]. Viallet et al. [41] have reported that etoposide and DOX, two topoisomerase II inhibitors, inhibit the cytotoxicity of PTX in four of five human non-small-cell lung cancer lines. It has also been reported that the nature of the interaction between etoposide and PTX is schedule-dependent and that antagonism of cytotoxic activity occurs with simultaneous but not sequential exposure [28]. Although cytotoxic antagonism between DOX and PTX has not been reported in patients, a sequence-dependent antagonism of cytotoxicity between etoposide and PTX has been observed in patients [30]. Whether or not similar interactions between DZR and PTX may affect the antineoplastic efficacy of PTX is not known, but preclinical studies on combinations of these two drugs would be important for future clinical trials.

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