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Doxorubicin Cardiotoxicity in Children: Comparison of a Consecutive Divided Daily Dose Administration Schedule With Single Dose (Rapid) Infusion Administration

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Background. Doxorubicin cardiotoxicity remains a serious problem in children with malignancy. The present study was undertaken to determine if the administration of consecutive divided daily doses of doxorubicin would significantly reduce the likelihood of cardiotoxicity in children compared with a single dose administration regimen. ***Procedure.*** One hundred thirteen children (60 boys and 53 girls) received doxorubicin either by single dose infusion or by a consecutive divided daily dose schedule. The divided dose patients received one third of the total cycle dose over 20 minutes for 3 consecutive days. Patients treated according to a single dose schedule received the cycle dose as a 20-minute infusion. The mean doxorubicin dose was 341 mg/m^2. Patients were followed up for 4–180 months. There were 60 boys and 53 girls in the series. ***Results.*** Fifteen patients developed cardiacdysfunction, eight of whom died of progressive cardiac failure. There was no significant difference in the incidence of cardiac dysfunction between the divided and single dose infusion groups. More girls than boys developed cardiac dysfunction and more girls died of progressive cardiac failure; this difference was not statistically significant. The median time to the development of cardiac failure was 2 months. ***Conclusions.*** The divided dose regimen did not alter the incidence of cardiotoxicity. Other schedules should therefore be investigated. Our data suggest that, at similar cumulative doses, girls are more likely to develop cardiac dysfunction than are boys. If the sex-related difference is proved in larger series of patients, it may be prudent to lower the recommended cumulative doses for girls. Med. Pediatr. Oncol. 31:512–515, 1998.

Key words: doxorubicin cardiotoxicity; chemotherapy complication; supportive care

INTRODUCTION

Doxorubicin is an anthracycline antibiotic with considerable antineoplastic activity [1]. It constitutes an important component of therapy for a variety of hematologic malignancies and solid tumor and is often used in pediatric patients for both initial induction therapy and reinduction therapy following relapse of malignancy. However, the therapeutic potential of this important agent is compromised by a cumulative, dose-related, potentially fatal, and often irreversible cardiac toxicity.

Doxorubicin-associated cardiotoxicity has been extensively studied. Toxicity is relatively rare in adults treated with doxorubicin up to a cumulative dosage of 300 mg/m^2, but the frequency of toxicity increases as the cumulative dose increases above this level. It occurs in approximately 5% of patients who receive more than 450 mg/m^2 [1–4]. Toxicity occurs at lower cumulative doses at extremes of age, however, and it is augmented in a synergistic fashion when doxorubicin is given sequentially or concomitantly with other cardiotoxic chemotherapeutic agents or with radiation therapy [5,6]. If cardiac toxicity is recognized promptly and further use of the drug is curtailed, life-threatening cardiotoxicity may be prevented; if therapy with doxorubicin is continued, however, cardiac toxicity will progress relentlessly and result in death from congestive heart failure [3]. Late toxicity in children, occurring months or years following administration of the drug, has been described and may result from additional insults or stresses to an already damaged myocardium, it may be due to ongoing myocyte damage, or it may result from both processes [7,8]. The threshold for late toxicity has recently been evaluated; late cardiac dysfunction is uncommon in children who received cumulative doxorubicin doses of 300 mg/m^2 or less [9].

As the cardiac effects of doxorubicin have become

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better understood, guidelines have evolved for use of the drug such that cardiac damage is kept to an acceptable level. However, these guidelines are neither universally accepted nor have they been totally successful in eliminating doxorubicin cardiotoxicity. The single most important measure in preventing potentially life-threatening cardiac toxicity has been limiting the total cumulative dose [3]. As children show a greater sensitivity to the cardiotoxic effects of doxorubicin than do adults, the drug may be stopped at relatively low cumulative dosages, even though the tumors may still be responding to treatment. A serious clinical dilemma is sometimes seen, where either a potentially less effective regimen is substituted for the doxorubicin regimen in a responding patient or doxorubicin is continued, carrying with it an increased risk of potentially life-threatening cardiac damage.

Measures to reduce the likelihood of cardiotoxicity of doxorubicin have received considerable attention and have included restricting the total cumulative dose, using pharmacological protectors, and modifying the administration schedule. The most interesting protector is the iron chelator dexrazoxane (Zinocard®) [10] (also known as ICRF-187 and ADR-529), a bisdiketopiperazine that has recently been approved for clinical use in the United States for the treatment of patients with breast cancer who have received at least 300 mg/m^2 of doxorubicin without the protector and who are to receive additional therapy [10,11]. However, concerns have been raised regarding a reduced oncologic effect of the doxorubicin/dexrazoxane combination [11]. There has also been very limited experience with dexrazoxane in children, underscoring the need for additional studies in this age group; the drug has not yet been approved for use in pediatric patients.

Continuous infusion administration schedules reduce cardiotoxicity. They have been extensively studied in the adult population and are well established. Doxorubicin may be given weekly or by prolonged (24–96-hour continuous) infusion; such schedules are associated with lower peak plasma concentrations of a factor considered of primary importance in the development of cardiotoxicity [12,13]. There appears to be no measureable change in the oncologic effect of doxorubicin with continuous infusion administration. Prolonged infusions, however, require infusion pumps and are less convenient than regimens using standard infusion. It was, therefore, hoped that a consecutive, divided daily dose infusion schedule might have some of the advantages of continuous infusion and also allow more convenient scheduling.

We report our retrospective observations regarding the incidence and severity of cardiotoxicity in a group of 113 pediatric patients treated with doxorubicin by single dose or by consecutive, divided daily dose administration schedules.

MATERIALS AND METHODS

The patient population in this study consisted of 113 consecutively registered, previously untreated children. There were 60 boys and 53 girls who were treated between January 1, 1979, and December 31, 1990. All were newly registered patients entered into a series of protocols designed to treat osteosarcoma and rhabdomyosarcoma. None of the patients showed evidence or preexisting cardiac disease or any form of cardiac dysfunction prior to receiving doxorubicin. Their age ranged from 1 to 17 years (mean, 10.6; median, 11) and the cumulative doxorubicin dose ranged from 113 to 506 mg/m^2 (mean cumulative dose, 341 mg/m^2). Doxorubicin was administered either by a consecutive, divided daily dose schedule, whereby one third of the cycle dose was given over 20 minutes on each of 3 consecutive days (96 patients) or by standard (single-dose) infusion administered over 20 minutes every 3 weeks (17 patients). Patients were assigned to one or the other of the treatment schedules entirely on the basis of the protocols that were available for the treatment of their primary diseases, accounting for the differences in the sizes of the two groups. Cardiac status or risk factors did not play a role in protocol selection; there were no differences in the protocols that would have affected the likelihood of doxorubicin cardiotoxicity.

Patients were given 60–75 mg/m^2 of doxorubicin in each cycle. The mean cumulative dose was 324 mg/m^2 for the divided dose group and 299 mg/m^2 for the single dose infusion group. The difference in the cumulative doses between the two groups was not significant ($P = 0.71$). All patients received doxorubicin in combination with other agents, including cyclophosphamide (67 patients), d-actinomycin (39 patients), cisplatin (*cis*-diamminedicloroplatinum-II, 48 patients), and methotrexate (53 patients). The differences in the number of patients who received these agents and the dosages received did not differ significantly between or within the two groups. Sixteen patients (14%) were treated concomitantly or sequentially with radiation therapy (100–9,794 rad). Neither the radiation dose nor the proportion of patients who underwent radiation therapy differed between the two groups; the cumulative dose of doxorubicin for patients who did and did not receive radiation therapy was 297 and 321 mg/m^2, respectively ($P = 0.35$).

Treatment was administered over a 6–9-month period and patients were followed up for 4–180 months. The mean total cumulative dose was 317 mg/m^2 for the boys and 324 mg/m^2 for the girls; this difference was not significant ($P = 0.36$).

Cardiac monitoring in this study consisted of determination of fractional shortening by M-mode echocardiography performed using standard protocols. All patients

TABLE I. Comparison of Consecutive, Divided Daily Dose and Standard Infusion Groups

	Consecutive, divided daily dose group	Single dose infusion group
No. of patients	96	17
Doxorubicin dose (mg/m^2)	324	299
Developed cardiac dysfunction	13 (13.5%)	2 (11.8%)

TABLE II. Sex-Related Differences Between Pediatric Patients Receiving Doxorubicin

Doxorubicin dose by gender for all patients (n = 113)

	Mean age (yrs)	Mean doxorubicin dose (mg/m^2)	Cardiac dysfunction (n)
Girls (n = 53)	11.4	324	9
Boys (n = 60)	9.9	317	6

Cardiac dysfunction subgroup (n = 15)

	Mean age	Mean doxorubicin dose	Cardiac deaths
Girls (n = 9)	11.3	421	5
Boys (n = 6)	9.8	435	3

Cardiac death subgroup (n = 8)

	Mean age	Mean doxorubicin dose
Girls (n = 5)	10.6	458
Boys (n = 3)	10.6	460

underwent baseline studies and were evaluated sequentially during the period of observation. A decrease in fractional shortening of more than 15% from the baseline value defined cardiac dysfunction. Statistical analysis was done using paired *t* tests and one-way analysis of variance. Informed consent was obtained for all participants according to institutional guidelines.

RESULTS

Fifteen of the 113 patients developed evidence of cardiac dysfunction as shown by significantly decreased fractional shortening on cardiac ultrasound studies. Nine were girls and six were boys. Cardiac dysfunction developed 1–23 months (median, 2 months) following the cessation of treatment. As expected, the mean cumulative doxorubicin dose in the patients who developed cardiac dysfunction was significantly higher than that in patients who did not experience cardiac dysfunction (426 and 317 mg/m^2, respectively, $P < 0.0001$). Of the 15 patients who developed cardiac dysfunction, 13 were in the divided daily dose group. These 13 patients received a mean cumulative doxorubicin dose of 434 mg/m^2 and constituted 13.5% of the total patients in the group. The remaining two patients who experienced cardiac dysfunction received doxorubicin by single dose infusion and constituted 11.8% of the single dose infusion group. These two patients received 300 and 450 mg/m^2, respectively. Of the 15 children who developed cardiac dysfunction, 9 were girls and 6 were boys.

Eight of the 15 patients with cardiac dysfunction (53%) ultimately died of progressive cardiac failure. Five of the deaths occurred in girls, accounting for 9.4% of the total female population; the three boys who died constituted 5% of the total male population. Table I compares and summarizes the data from the consecutive, divided daily dose and single dose infusion groups; Table II summarizes the sex-related differences in the patients who developed cardiac dysfunction.

DISCUSSION

Previous studies have suggested that doxorubicin cardiotoxicity is unusual at cumulative doses below 300 mg/m^2 and occurs in about 5% of adult patients given a cumulative dose of 400–450 mg/m^2 [1–4]. It is also clearly established that children and adult patients who receive radiation therapy are at increased risk for cardiotoxicity. Nevertheless, the 13% incidence of cardiac dysfunction and 7% mortality in our patients is disturbing. The fact that modifying the schedule by giving doxorubicin in divided daily doses, as was done in most patients in our series, did not decrease either the incidence of cardiac dysfunction or the mortality due to cardiac dysfunction is discouraging. Despite the difference in the numbers of patients in the two administration schedule groups and the relatively small number of patients in the single dose infusion group, no statistical difference could be found ($P = .99$). While a remote possibility that a type II error exists, and could be detected by a much larger investigational sample, such variance would not alter the conclusion that neither of the two schedules studied has a clinically relevant advantage over the other with regard to cardiotoxicity.

It has been suggested that the oncologic effect of doxorubicin is related to the cycle dose and the total cumulative dose administered, whereas the cardiotoxic effects are related more to the peak plasma levels and the total cumulative dose. This has prompted introduction of continuous infusion administration schedules used in adults, which has been accompanied by a significant reduction in the incidence of cardiotoxicity [10]. It was hoped, therefore, that the 3-day divided schedule would reduce peak plasma levels sufficiently to decrease the incidence of cardiac toxicity in our pediatric population, thereby allowing a greater cumulative dose of doxorubicin to be given while keeping the incidence of severe cardiac dysfunction and cardiac mortality at an acceptable level. The decrease in the incidence of cardiotoxicity

noted in adults treated with continuous infusion doxorubicin was, unfortunately, not observed with the consecutive, divided daily dose administration schedule used in the treatment of our series of children.

It is interesting to note that despite receiving similar cumulative doxorubicin doses, more girls than boys in our series developed cardiac dysfunction. This finding has also been reported by others [14]. While there are insufficient patients to prove a sex-related difference, our data do support the previous study suggesting that girls may be at higher risk than boys for developing doxorubicin toxicity. Once cardiotoxicity was established, about one half of the patients, (five of the nine girls and three of the six boys), died of progressive cardiac dysfunction.

Our data confirm that doxorubicin toxicity in children continues to be a serious problem and that administration in consecutive, divided daily doses does not significantly reduce the incidence of toxicity. Further studies using other schedules, especially continuous infusion schedules, and cardiac protectors in children are clearly warranted. A sex-related difference in the incidence of cardiac toxicity is supported by our findings and suggests that future efforts, perhaps using techniques of meta-analysis, may define a lower safe total cumulative dose of doxorubicin for girls. Finally, once doxorubicin cardiotoxicity is established in children, it is associated with considerable mortality, resulting in the death of about one half of those afflicted. Even with careful clinical and ultrasonographic monitoring, the problem of doxorubicin cardiotoxicity in children has not been resolved satisfactorily.

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