Cyclophosphamide Cardiotoxicity: An Analysis of Dosing as a Risk Factor

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Patients who undergo bone marrow transplantation are generally immunosuppressed with a dose of cyclophosphamide (CYA) which is usually calculated based on the patient’s weight. At these high doses of CYA, serious cardiotoxicity may occur, but definitive risk factors for the development of such cardiotoxicity have not been described. Since chemotherapeutic agent toxicity generally correlates with dose per body surface area, we retrospectively calculated the dose of CYA in patients transplanted at our institution to determine whether the incidence of CYA cardiotoxicity correlated with the dose per body surface area. Eighty patients who were to receive CYA 50 mg/kg/d for four days as preparation for marrow grafting underwent a total of 84 transplants for aplastic anemia, Wiskott-Aldrich syndrome, or severe combined immunodeficiency syndrome. Fourteen of 84 (17%) patients had symptoms and signs consistent with CYA cardiotoxicity within ten days of receiving 1 to 4 doses of CYA. Six of the 14 patients died with congestive heart failure. The dose of CYA per body surface area was calculated for all patients and the patients were divided into two groups based on daily CYA dose: Group 1, CYA <1.55 g/m²/d; Group 2, CYA >1.55 g/m²/d. Cardiotoxicity that was thought to be related to CYA occurred in 1/32 (3%) of patients in Group 1 and in 13/52 (25%) patients in Group 2 (P < 0.025). Congestive heart failure caused or contributed to death in 0/32 patients in Group 1 and 6/52 (12%) of patients in Group 2 (P < 0.25). There was no difference in the rate of engraftment of evaluable patients in the two groups (P > 0.5). We conclude that the CYA cardiotoxicity correlates with CYA dosage as calculated by body surface area, and that patients with aplastic anemia and immunodeficiencies can be effectively prepared for bone marrow grafting at a CYA dose of 1.55 g/m²/d for four days with a lower incidence of cardiotoxicity than patients whose CYA dosage is calculated based on weight. This study reaffirms the principle that drug toxicity correlates with dose per body surface area.

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In order to achieve successful bone marrow engraftment, effective immunosuppression of the bone marrow recipient is of paramount importance. Cyclophosphamide (CYA) is an alkylating agent that has been shown to have both potent immunosuppressive properties and antineoplastic activity, and it is a mainstay in most pretransplant preparative regimens. In 1970, Storb and colleagues investigated the hematologic and pathologic effects of various high-dose CYA regimens in rhesus monkeys. Monkeys given 240 mg/kg of CYA over one to four days had a greater than 75% incidence of cardiotoxicity. Subsequently, in 1971, Santos et al reported the first case of fatal CYA cardiotoxicity in a human. Since 1971, two series and numerous case reports have appeared in the literature, indicating that cardiotoxicity can occur in patients receiving 120 to 270 mg/kg of CYA over one to eight days. These patients developed severe and often fatal congestive heart failure soon after the first dose of CYA. Unfortunately, it is difficult to determine the true incidence and contribution of CYA to the cardiotoxicity since the literature contains primarily case reports and the CYA was administered in various dosages and often with other potentially cardiotoxic agents. However, if the series of Steinherz et al and Gottardi et al are combined, the incidence of symptomatic cardiomyopathy is 22% (16/72) and fatal cardiotoxicity is 11% (8/72).

It is noteworthy that there are no case reports of fatal cardiotoxicity in humans less than 12 years old, suggesting that there is either an intrinsic resistance to the cardiotoxic effects of CYA in children or that children received a lower relative dose of CYA. In most bone marrow transplant protocols CYA is administered on a mg/kg basis, even though chemotherapeutic agent toxicity in general and CYA toxicity in particular have been shown to correlate with dose per body surface area. We retrospectively analyzed the occurrence of cardiotoxicity in patients with aplastic anemia and immunodeficiency syndromes treated at our institution over the last 13 years. We chose patients with aplastic anemia or immunodeficiency syndromes because we used the same dosage of CYA to prepare patients with these diseases for marrow transplantation, and we avoided the confounding effects of prior anthracycline use and total body irradiation which are used in patients with malignancies. This article summarizes our analysis of CYA dosing and cardiotoxicity in 80 patients undergoing a total of 84 marrow transplants.

METHODS

In accordance with institutional review board guidelines, we reviewed the records of 80 consecutive patients with aplastic anemia, severe combined immune deficiency syndrome (SCIDS), and the Wiskott-Aldrich syndrome (WAS) who received high-dose CYA as part of the preparative regimen for bone marrow transplantation between 1972 and 1985 at the Brigham and Women’s Hospital and the Children’s Hospital Medical Center in Boston. Patients who received total body irradiation or who had known prior heart disease were excluded from the analysis. The only patients with SCIDS who were prepared with CYA received T cell-depleted marrow inocula.
from haploidentical family members. These patients received or were scheduled to receive CYA at a dosage of 50 mg/kg/d for four consecutive days. Other immunosuppressive and myelotoxic agents are listed in Table 1; these regimens have been reported previously. In brief, 49 patients with aplastic anemia received rabbit antithymocyte serum (ATS) 0.2 mL/kg every other day for 3 doses, procarbazine 12.5 mg/kg every other day for 3 doses, and CYA 50 mg/kg/d for four days; 15 patients were prepared with CYA 50 mg/kg/d for four days alone, and one patient with aplastic anemia complicating paroxysmal nocturnal hemoglobinuria received busulfan 16 mg/kg in divided doses in addition to the CYA, ATS, and procarbazine. Children with SCIDS receiving haploidentical, T cell-depleted marrow transplants were treated similarly to patients with aplastic anemia except they did not receive the procarbazine.

The patients with WAS received ATS, CYA 50 mg/kg/d for four days, and busulfan 8 to 16 mg/kg in divided doses. All but one patient with aplastic anemia were transplanted from HLA identical, MLR compatible siblings; the only exception was a patient with a D/DR crossover, and thus, a single antigen mismatch. Patients with WAS were transplanted from either HLA identical or haploidentical relatives and all haploidentical transplants were performed with T cell-depleted marrow (Table 1).

Cyclophosphamide cardiotoxicity was defined as the occurrence of symptomatic congestive heart failure within ten days of receiving the first dose of CYA. All such patients were followed with frequent chest x rays and electrocardiograms. Routine post-transplant echocardiograms were not obtained. Engraftment was assessed by the recovery of granulocytes to >500 cells/µL, platelets >20,000 cells/µL without platelet transfusions, reticulocytes >1%, red blood cell typing for 30 RBC antigens, cytogenetics, DNA polymorphism analysis, and blastogenic response to lectins as described previously.

Statistical methods. χ² analysis and Student's t test were performed with the Systat statistical software package (Evanston, Ill), and the life-table analysis and log-rank test were performed as described by Peto et al. All χ² analyses utilized the Yates continuity correction.

RESULTS

Patient characteristics. The age, sex, diagnoses, HLA compatibility, and preparative regimens are shown in Table 1. Eighty patients underwent 84 evaluable transplants (2 patients with aplastic anemia and 2 patients with SCIDS each received 2 transplants). Sixty-three patients had severe aplastic anemia, 10 patients had SCIDS, and 7 patients had WAS.

Four of the patients had aplastic anemia as a complication of paroxysmal nocturnal hemoglobinuria and none had Fanconi's anemia. Because of the nature of the diseases, patients with WAS and SCIDS were significantly younger than the patients with aplastic anemia (Student's t test, P < 0.01).

Incidence of cyclophosphamide cardiotoxicity. In 14/84 (17%) transplants, signs and symptoms consistent with congestive heart failure developed within ten days of receiving the first dose of CYA. The clinical diagnosis of congestive heart failure was supported by echocardiography in 6 patients and was equivocal in 2. Six of the 14 (43%) died with congestive heart failure, although in 4/6 sepsis may have contributed. Postmortem examinations were obtained in 4 of the 6 patients and findings consistent with CYA cardiotoxicity were present in all four. In none of the cases that came to autopsy was there evidence of cardiac hemosiderosis. All of the cases of congestive heart failure were found in the group with aplastic anemia (14/65 [22%]); no patients with SCIDS or WAS developed clinical cardiotoxicity (0/19).

Correlation of age and dose per body surface area with the occurrence of cardiotoxicity. Patients with cardiotoxicity were significantly older than patients without clinically apparent cardiac injury (median ages 18 years < 2 years; Student's t test, P < 0.01). When cardiotoxicity did occur in children it was not fatal. Since small patients have a greater relative body surface area, we recalculated the dose of CYA that they received based on body surface area. The dose of CYA was 1.822 ± 0.203 g/m²/d (mean ± SD) in patients with cardiotoxicity and 1.532 ± 0.380 g/m²/d (mean ± SD) in patients without cardiac toxicity (Student's t test, P < 0.005). The relationship of age and dose/m² is shown in Fig 1. It is clear that children received much lower relative doses of CYA than did adults and adolescents. Because some patients developed cardiotoxicity before the entire dose of 200 mg/kg was administered, data were analyzed based on daily dosage rather than total dosage. The relationship between cardiotoxicity and dose per body surface area is shown in Fig 2. Since there was a dose of CYA below which it

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Abbrev: Ara-C, arabinosyl cytosine; ATS, antithymocyte serum; Bu, busulfan; CYA, cyclophosphamide; PC, procarbazine; SCIDS, severe combined immunodeficiency syndrome.

*Numbers in parentheses indicate the number of transplants done with the indicated regimen. Two patients with aplastic anemia and two patients with SCIDS were transplanted twice.
appeared unlikely that a subject would develop cardiotoxicity, the patients were divided into two groups based on the daily CYA dose: Group 1 received CYA $\leq$ 1.55 g/m²/d and Group 2 received CYA $>1.55$ g/m²/d. The median age of the patients in Group 1 was two years (range 4/12 to 26 years) while the median age in Group 2 was 18 years (range 17 to 52 years) and this difference was statistically significant (Student's $t$ test, $P < 0.01$). Cardiotoxicity occurred in 1/32 (3%) patients in Group 1 compared to 13/52 (25%) of patients in Group 2 ($x^2 = 5.34$, $P < 0.025$). When the patients with aplastic anemia were analyzed separately, cardiotoxicity occurred predominantly in the patients in Group 2 (13/52 vs 1/13, $x^2 = 0.85$, $P > 0.25$). Although the analysis did not reach statistical significance, the trend suggests that the difference would have been significant if more patients were studied.

It is important to note that we did not observe cumulative CYA cardiotoxicity in the 4 subjects who received more than one transplant and therefore received CYA 400 mg/kg total dose. However, it is possible that cumulative toxicity might be apparent if more patients are studied. Congestive heart failure caused or contributed to death in 0/32 patients in Group 1 vs 6/52 (12%) of patients in Group 2 ($x^2 = 2.43$, $P < 0.25$).

**Engraftment.** Patients were considered evaluable for determination of engraftment if they lived for at least 21 days after transplant. Since the patients with SCIDS received haploidentical transplants and were likely to develop only lymphoid grafts, and the children with WAS received busulfan, we only analyzed the evaluable individuals with aplastic anemia in Groups 1 and 2. In Group 1, 9/10 (90%) of the patients engrafted compared with 33/41 (81%) of the patients in Group 2 ($x^2 = 0.06$, $P > 0.5$). There was also no difference in survival when assessed by life-table analysis and the log-rank test ($x^2 = 1.012$, $P > 0.5$). It is possible that differences in engraftment would be apparent if more patients were studied; however, our data do not suggest a trend toward a higher rate of engraftment with higher doses of CYA.

**DISCUSSION**

In the early 1970s Santos and coworkers$^4$ and the Seattle group$^3$ pioneered the use of cyclophosphamide in the immunosuppression of patients in preparation for bone marrow grafting. Cyclophosphamide was generally administered in a total dose of 200 mg/kg for patients with aplastic anemia and 120 mg/kg for patients with malignancies who would also receive total body irradiation. Based on those early studies most transplant units, including ours, employed similar preparative regimens. It became gradually clear that this dose of cyclophosphamide could cause a lethal cardiotoxicity characterized by severe, often refractory, congestive heart failure occurring one to ten days after the administration of the first dose of cyclophosphamide.$^3,14$ The clinical syndrome of severe congestive heart failure was accompanied by electrocardiographic findings of diffuse voltage loss, cardiomyopathy, pulmonary vascular congestion, and pleural effusions on chest radiograph, and echocardiographic demonstration of decreased fractional ventricular wall shortening, increased end-diastolic volume, and pericardial effusions. Pathological examination of the heart reveals hemorrhagic myocardial necrosis, thickening of the left ventricular wall, serosanguinous pericardial effusions, and fibrinous pericarditis. Electron microscopy has shown multifocal myocardial necrosis associated with fibrin microthrombi near areas of capillary endothelial damage. These findings are thought to be consistent with myocardial necrosis following cyclophosphamide-induced endothelial damage.$^6$
No definitive risk factors for the development of CYA cardiotoxicity have yet been identified. It does not seem to be related to the underlying disease or anemia or thrombocytopenia. It is possible that prior anthracycline chemotherapy and/or radiation therapy may predispose to the development of CYA cardiotoxicity. However, we excluded from evaluation all patients who had received anthracyclines or any radiation therapy, and in the absence of any demonstrable prior cardiac dysfunction it is likely that the cardiomyopathy observed in this series is due to CYA alone. Although procarbazine is not known to be associated with cardiotoxicity, fewer children received it as part of the preparatory regimen and we cannot exclude the possibility that procarbazine can contribute to the cardiotoxicity of CYA. Clearly, sepsis can be associated with cardiac dysfunction, and since 4/6 patients who died were septic, it is likely that sepsis contributed to the severity of the cardiac damage. Cardiac injury due to transfusion-associated iron overload could conceivably predispose patients to CYA-induced cardiotoxicity; however, none of our patients who died had iron deposition in the heart, and most patients with aplastic anemia who have an acceptable donor are transplanted before they have received the 50 or more units of red blood cells required to produce hemosiderosis.

The rationale for using CYA at a dosage of 200 mg/kg is based both on prior animal studies and the observation that 180 mg/kg used alone to prepare patients with acute lymphoblastic leukemia for marrow transplant resulted in a high relapse rate. However, the extrapolation of animal studies to humans is often difficult. In 1958, Pinkel et al showed that the effects of chemotherapeutic agents on animals and humans were similar when the dose was calculated as dose per unit of body surface area, but quite dissimilar when calculated per unit of weight. Freireich and colleagues subsequently made a quantitative comparison of the toxicity of multiple anticancer agents including CYA in the mouse, rat, hamster, dog, monkey, and man. They also observed that the toxicities were quite similar between species when dose was calculated based on body surface area.

We observed an extremely low incidence of CYA cardiotoxicity in our pediatric patients. Since children have a relatively smaller ratio of weight to body surface area than do adults, we hypothesized that the children were actually receiving relatively less CYA than the adult patients. Furthermore, by similar analysis obese patients were likely to be overdosed when treated on a mg/kg basis. This suspicion was confirmed when we calculated the CYA dose based on body surface area. Thus, the dose of CYA administered ranged from 0.75 mg/m²/d to 2.35 mg/m²/d, and this range was due largely to age related difference in body surface area (Fig 1). Cardiotoxicity was significantly more likely to occur at a CYA dose of >1.55 g/m²/d (Fig 2). However, it did not appear that the lower dose compromised the transplant. There was no dose-related difference in the rate of engraftment or survival between the two groups. In this retrospective analysis, it can be argued that the lower incidence of cardiotoxicity in the younger patients is due to an intrinsic, age-related difference in the susceptibility to CYA-induced heart damage. However, the data presented cannot address that concern since inferences about relative susceptibility to drug effects can only be made if the dosing is the same.

This analysis suggests that cyclophosphamide cardiotoxicity is dose related and that patients with aplastic anemia, SCIDS, and WAS can be effectively prepared for marrow grafting with CYA 1.55 g/m²/d for 4 consecutive doses with equivalent likelihood of engraftment and less cyclophosphamide cardiotoxicity. It is likely that a similar change in dosing would reduce the incidence of cardiotoxicity in patients transplanted for malignancies.

REFERENCES

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