Assessment of Left Ventricular Dysfunction in Children Undergoing Chemotherapy

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Background: In Taiwan, children with malignancies are treated under the protocols of the Taiwan Pediatric Oncology Group (TPOG). The purpose of this study was to determine the change in left ventricular (LV) function in pediatric patients undergoing chemotherapy.

Methods: A total of 19 pediatric patients (mean age, 12.5 ± 4.6 years; 11 males, 8 females) were enrolled. We divided the patients into 2 groups: (1) osteogenic sarcoma (OGS) group (n = 12; Group I); and (2) non-osteogenic sarcoma (non-OGS) group (n = 7; Group II). The accumulated dosages of anthracycline in Group I and II patients were 144.3 ± 56.4 mg/M^2 and 131.7 ± 105.5 mg/M^2 (p = 0.735), respectively. The children received echocardiography to investigate the parameters of LV systolic function, LV diastolic function, and myocardial performance index (MPI) after the entire chemotherapy course.

Results: Higher E/A ratio (1.71 ± 0.37), shorter isovolumic relaxation time (IRT, 42 ± 19.14 ms), and shorter deceleration time (DT, 140.3 ± 40.6 ms) were demonstrated in these patients. There was no statistically significant difference in the E/A ratio and DT between the 2 groups. Group I children were older (14.4 ± 3.7 *vs.* 9.3 ± 4.5 years; p = 0.015) and had lower MPI (0.20 ± 0.02 *vs.* 0.28 ± 0.07; p = 0.031) than Group II children.

Conclusion: The children treated with chemotherapy using the TPOG protocol had a shorter IRT, higher E/A ratio and shorter DT. No significant evidence of anthracycline-related cardiotoxicity was found in any of the children in this study undergoing chemotherapy with the TPOG protocol. [*J Chin Med Assoc* 2007;70(6):241–244]

Key Words: anthracycline, chemotherapy, children, left ventricular dysfunction

Introduction

In Taiwan, children with malignancies who need chemotherapy management are treated according to Taiwan Pediatric Oncology Group (TPOG) protocols. Under the individual protocols, those children ought to receive intravenous fluid hydration, serum alkalization and the administration of various chemotherapy agents. Some chemotherapy agents, especially anthracycline, have been demonstrated to be associated with cardiotoxicity associated with delayed myocardial damage that depends on the accumulated dosage.[1,2] However, information on the influence of chemotherapy agents on cardiac function in children with malignancies is limited. The purpose of this study was to determine the change in left ventricular (LV) function in children with malignancies undergoing long-term chemotherapy.

Methods

Study population

A total of 19 pediatric patients (mean age, 12.5 ± 4.6 years; 11 males, 8 females) with malignancies were enrolled. We divided the patients into 2 groups: (1) an osteogenic sarcoma (OGS) group (n = 12; Group I); and (2) a non-osteogenic sarcoma (non-OGS) group (n = 7; Group II), which included acute lymphoblastic/myeloblastic leukemia (ALL/AML, n = 4), neuroblastoma (NB, n = 2) and non-Hodgkin's lymphoma (NHL, n = 1). All children had received standard chemotherapy using the TPOG protocol with or without low-to-moderate doses of anthracycline (for osteogenic sarcoma).[3] The accumulated dosages of anthracycline in Group I and II patients were 144.3 ± 56.4 mg/M^2 and 131.7 ± 105.5 mg/M^2 (p = 0.735), respectively.

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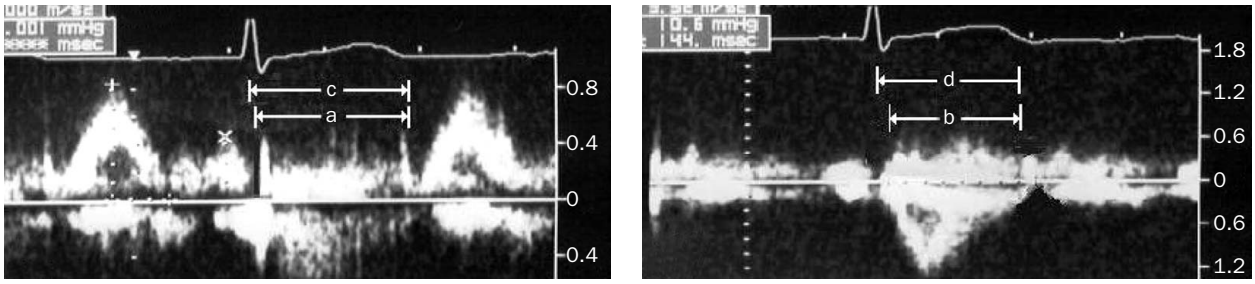

IRT = c – d; ICT = (a – b) – IRT
MPI = (IRT + ICT)/ET = (a – b)/b

Figure 1. Doppler intervals were measured in a 4-chamber apical scan plane for interval "a" (from the cessation to onset of the mitral inflow), and in the 5-chamber apical view, scan plane was also performed for interval "b" (equal to the ejection time; ET). Myocardial performance index (MPI) was defined as the sum of the isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by the ejection time (ET), i.e. MPI = (ICT+IRT)/ET; MPI = (a – b)/b. To account for a slight variation in the R-R cycle length, each time interval was measured for 3–5 consecutive beats and then averaged. Interval "c" is from the R-wave to the onset of mitral inflow, and interval "d" is from the R-wave to the cessation of left ventricular outflow. Associated with "c" and "d", we could calculate IRT by the formula IRT = c – d.

After completion of the entire chemotherapy course, the children received echocardiography to investigate the various parameters of LV systolic function, diastolic function, and myocardial performance index (MPI). We compared the systolic and diastolic parameters of LV function and MPI between the 2 groups.

Echocardiographic examination

Complete 2-dimensional spectral Doppler and color flow Doppler examinations were performed in all patients. The Doppler measurements were performed using a 4- or 8-MHz transducer as appropriate for patient size, and an HP ultrasound system (Hewlett Packard M2424A) was utilized. The Doppler signals were displayed at a paper speed of 100 m/s. The basic indicators of systolic function, including LV ejection fraction/fractional shortening (EF/FS), and rate-corrected mean velocity of the circumferential fiber shortness (Vcf) were measured according to the recommendations of the American Society of Echocardiography.[4]

The indicators of diastolic function for the transmitral peak velocities of early (E) and late (A) diastole, E/A ratio, and deceleration time (DT) were measured by pulse-wave Doppler technique.[5] The specific time intervals measured for delivering the MPI (Tei index) are shown in Figure 1. The Doppler intervals were measured in a 4-chamber apical scan plane for interval "a" (from the cessation to onset of the mitral inflow), and in the 5-chamber apical view, scan plane was also performed for interval "b" (equal to the ejection time; ET). MPI was defined as the sum of the isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by the ejection time (ET), i.e. MPI = (ICT + IRT)/ET; MPI = (a – b)/b. ICT was calculated from the cessation of mitral inflow to the onset of aortic outflow. IRT was calculated from the cessation of aortic outflow to the onset of mitral inflow. To account for any slight variation in the R-R cycle length, each time interval was measured for 3–5 consecutive beats and then averaged.

Statistical analysis

All data are expressed as mean ± standard deviation (SD). Student's *t* test was used for statistical analyses and comparisons between the 2 groups. Collected data that were not normally distributed were compared using the Mann-Whitney Rank Sum test. Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics

The clinical characteristics are presented in Table 1. The 19 patients (11 males, 8 females) had a mean age of 12.5 ± 4.6 years, mean body weight of 39.8 ± 15.6 kg, mean height of 146.0 ± 22.9 cm and mean body mass index (BMI) of 1.77 ± 0.32. There were no statistical differences in the body weight, height or BMI between Group I and Group II patients, but Group II patients were younger (14.4 ± 3.6 *vs.* 9.2 ± 4.5 years old; $p = 0.015$). While the study reported that all the patients in the OGS group had completed neoadjuvant chemotherapy, 9 had undergone the TPOG protocol with no lung metastases and 3 had completed the TPOG protocol with lung metastases. Four patients with ALL/AML who had undergone the TPOG protocol were in complete remission (2 AML patients underwent peripheral blood stem cell transplantations). The other

Table 1. Demographic data of patients in the osteogenic sarcoma group (Group I) and the non-osteogenic sarcoma group (Group II)

	All	Group I	Group II	*p* (Group I *vs.* II)
Age (yr)	12.5 ± 4.6	14.4 ± 3.6	9.2 ± 4.5	0.015*
Gender (male/female)	11/8	7/5	4/3	0.661
Body weight (kg)	39.7 ± 15.6	43.5 ± 12.9	33.5 ± 18.7	0.187
Height (cm)	146.0 ± 22.9	155.0 ± 14.8	130.5 ± 27.1	0.057
Body mass index	1.77 ± 0.32	1.76 ± 0.32	1.79 ± 0.36	0.875

**Significant difference.*

Table 2. Parameters of left ventricular systolic and diastolic function in the osteogenic sarcoma group (Group I) and the non-osteogenic sarcoma group (Group II)

	All	Group I	Group II	*p* (Group I *vs.* II)
Systolic parameters				
LVEF (%)	72.0 ± 5.7	73.0 ± 6.1	70.3 ± 5.1	0.314
LVFS (%)	40 ± 4.8	40.7 ± 4.8	38.9 ± 4.9	0.448
Mean Vcf (1/s)	1.55 ± 0.20	1.54 ± 0.25	1.56 ± 0.31	0.923
Diastolic parameters				
E/A ratio	1.71 ± 0.37	1.72 ± 0.4	1.69 ± 0.3	0.911
DT (ms)	140.3 ± 40.6	155.1 ± 42.1	114.9 ± 22.6	0.099
MPI	0.23 ± 0.06	0.20 ± 0.02	0.28 ± 0.07	0.031*
IRT (ms)	42.00 ± 19.14	36.52 ± 13.63	51.38 ± 24.42	0.220
ICT (ms)	18.15 ± 9.74	17.77 ± 8.43	18.81 ± 12.40	1.00
ET (ms)	261.03 ± 28.83	265.16 ± 24.54	253.95 ± 36.01	0.429

**Significant difference. LVEF = left ventricular ejection fraction; LVFS = left ventricular fractional shortening; Vcf = velocity of the circumferential fiber shortness; DT = deceleration time; MPI = myocardial performance index; IRT = isovolumic relaxation time; ICT = isovolumic contraction time; ET = ejection time.*

2 with neuroblastomas were kept on consolidation therapy and were also in complete remission. The 1 patient with non-Hodgkin's-type lymphoma had been receiving the TPOG protocol and was in partial remission. Mean overall follow-up was 8.36 months (range, 1–18 months).

Echocardiographic examinations

Table 2 summarizes the echocardiographic data of LV systolic and diastolic function. Nineteen patients had normal LV systolic function with LVEF 72.0 ± 5.7%, LVFS 40 ± 4.8% and rate-corrected mean Vcf 1.55 ± 0.20 circumferences/s. However, there was a trend towards higher E/A ratio (1.71 ± 0.37) and shorter DT (140.3 ± 40.6 ms) in the patients receiving chemotherapy, but there was no statistically significant difference in E/A ratio and DT between the 2 individual groups. A significantly lower MPI (0.23 ± 0.06) with a tendency toward a shorter IRT (42.00 ± 19.14 ms) and shorter ICT (18.15 ± 9.74 ms) was also observed in these patients. Furthermore, Group I patients had an even lower MPI when compared with Group II patients (0.20 ± 0.02 *vs.* 0.28 ± 0.07; $p = 0.031$).

Discussion

According to previously published literature, anthracycline is the most common chemotherapy agent that may induce myocardial damage leading to systolic and diastolic dysfunction depending on the total accumulated dosage.[2,6,7] Dr Lubomir demonstrated the negative influence on the heart after anthracycline treatment in a study that included a total of 12 patients (8%) with LV systolic dysfunction (LVEF < 55%; LVFS < 30%).[1] According to a previous report by Billingham et al, it was determined that anthracycline cardiomyopathy developed on the basis of the structural changes observed in all the myocytes, which lead to subsequent vacuolation of the cytoplasm, myofibril wastage and fibrous degeneration of the myocardium.[8] All those changes had a linear relationship to the cumulative dosage of anthracycline, especially with high doses > 400–500 mg/M^2.[1,2,9] However, all the patients in our study had normal LV systolic function assessed by echocardiography (normal LVEF, LVFS and rate-corrected mean Vcf). The reason was possibly due to there not being a high enough cumulative dosage of

anthracycline in our patients. On the other hand, the significantly higher E/A ratio, shorter DT and shorter IRT demonstrated that the LV diastolic dysfunction was the result of a restricted filling pattern in both groups, but there was no statistically significant difference between the 2 groups. The results may imply that the reduced left ventricle compliance might not be completely attributed to anthracycline cardiotoxicity in the TPOG protocol in these patients, but could be associated with long-term fluid overloading or other chemotherapy agents.

MPI was first described by Dr Tei Chuwa in 1995 as a noninvasive Doppler measurement of the global (systolic and diastolic) ventricular function, and its normal range was 0.33 ± 0.02 for those aged between 3 and 18 years old.[10–12] A broad range of applications in cardiology were established in the literature, including those for congenital heart disease, valvular heart disease, cardiomyopathy, heart failure, pulmonary hypertension and cardiotoxicity from chemotherapy.[13–17] In the present study, both groups of children had a relatively low MPI (0.23 ± 0.06) with a relatively short IRT associated with a restricted filling pattern. The results were different from the effects of anthracycline on MPI observed by Ishii et al.[17] They reported a significantly higher MPI value (0.45 ± 0.06) associated with a prolongation of the IRT and ICT, and a considerable shortening of the ET in 30 patients administered moderate to high doses of anthracycline. By comparing the 2 patient groups in the present study, there was a statistical difference in MPI, but no differences in IRT, ICT and ET. These findings imply that there was no significant anthracycline-related cardiotoxicity in the children in this study because of the low accumulated dosage. However, a lower MPI in the patients in the OGS group was demonstrated, and further investigation is needed to explore possible reasons for this.

As only a limited number of patients were enrolled in these 2 groups, more studies are needed to investigate LV dysfunction in children undergoing chemotherapy with anthracycline.

We conclude that children with malignancies who underwent chemotherapy according to the TPOG protocol had normal LV systolic function. We also demonstrated LV diastolic dysfunction with a restricted filling pattern and shorter IRT, higher E/A ratio and shorter DT. The shorter IRT resulted in a lower MPI in all the children, especially in the OGS group. Fortunately, no significant evidence of anthracycline-related cardiotoxicity was found in any of the children undergoing chemotherapy according to the TPOG protocol in this study.

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