Notable Effects of Angiotensin II Receptor Blocker, Valsartan, on Acute Cardiotoxic Changes after Standard Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone

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BACKGROUND. There are three distinct types of doxorubicin-induced cardiotoxicity (acute, chronic, and late-onset). Although previous studies with animal models suggest that angiotensin II plays a key role in the process of the doxorubicin-induced cardiotoxicity, there has been no such observation in humans. This randomized study investigated whether valsartan, a new class of angiotensin II receptor blocker (ARB), can inhibit acute cardiotoxicity after doxorubicin-based chemotherapy.

METHODS. Forty consecutive patients with untreated non-Hodgkin lymphoma who were scheduled to undergo standard chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) (mean age, 56 yrs; range, 24–70 yrs) were randomized with minimization methods to receive CHOP with or without 80 mg/day of valsartan. Acute cardiotoxicity was comprehensively evaluated with neurohumoral, echocardiographic, and electrocardiographic markers before and on Days 3, 5, and 7 after the initiation of CHOP.

RESULTS. CHOP induced transient increases in the left ventricular end-diastolic diameter in an echocardiogram, the QTc interval and QTc dispersion in an electrocardiogram, and in the plasma brain and atrial natriuretic peptides. All these changes returned to nearly normal levels within a week after CHOP ($P < 0.001$). Notably, valsartan significantly prevented all these changes except for the elevation in atrial natriuretic peptide ($P < 0.05$). No significant change was observed in blood pressure or heart rate between the valsartan and control groups.

CONCLUSIONS. The results indicate that angiotensin II may play an essential role in acute CHOP-induced cardiotoxicity in humans. Future long-term studies are necessary to judge whether ARBs have a potential to prevent the chronic or late-onset types of doxorubicin-induced cardiotoxicity. ***Cancer* 2005;104:2492–8.**

KEYWORDS: acute cardiotoxicity, prevention, anthracycline, angiotensin II receptor blocker.

Standard chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) has been widely used as a first-line treatment for non-Hodgkin lymphoma.[1] However, doxorubicin used in CHOP is associated with significant cardiotoxicity.[2] Three distinct types of anthracycline-associated cardiotoxicity (acute, chronic, and late-onset) have been reported.[2] Acute cardiotoxicity appears immediately or up to weeks after the start of anthracycline administration. Although the clinical manifestations of acute cardiotoxicity are not well characterized, they include transient arrhythmias,

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ST/T changes in electrocardiogram, pericarditis-myocarditis syndrome, and in the most severe cases, acute cardiac decompensation.[3,4] Neurohumoral markers such as brain and atrial natriuretic peptides (BNP and ANP, respectively) may be the most sensitive markers of acute cardiotoxicity induced by anthracyclines.[5,6] Conversely, chronic cardiomyopathy, which usually develops within a year after the initiation of chemotherapy, is well documented. The cumulative dose of doxorubicin is known to be an important factor in dilated cardiomyopathy-like congestive heart failure.[7] Recently, we found that an electrocardiographic marker, QTc dispersion, is more sensitive than traditional cumulative anthracycline doses for evaluating the subclinical cardiac damage that may lead to acute heart failure in patients with hematologic disease who are exposed to high-dose chemotherapy and stem cell transplantation.[8,9] Finally, late-onset cardiotoxicity occurs years or decades after a long asymptomatic period, and typically presents with left ventricular dysfunction, heart failure, and arrhythmias.[10–12] Late-onset cardiotoxicity is becoming increasingly important, especially for young adults who are long-term cancer survivors.[2]

Angiotensin II (Ang II), an effector peptide of the renin–angiotensin system, plays a significant role in the pathophysiology of hypertensive and ischemic heart disease in humans.[13,14] Interestingly, in rats that had undergone short- or long-term administration of doxorubicin, coadministration of angiotensin-converting enzyme inhibitors are reported to almost completely prevent the decline in cardiac function as well as the increase in left ventricular weight induced by doxorubicin.[15–18] Furthermore, recent evidence has demonstrated that doxorubicin cannot induce cardiac injury in Ang II type I receptor gene knockout mice,[19] altogether indicating a key role of Ang II in the pathogenesis of doxorubicin-induced cardiotoxicity. However, to our knowledge, the role of Ang II in the doxorubicin-induced cardiotoxicity in humans is completely unknown. The aim of the current randomized study for patients with non-Hodgkin lymphoma was: 1) to characterize in more detail acute CHOP-induced cardiotoxicity using various echocardiographic and electrocardiographic as well as serum cardiac markers, and 2) to evaluate whether or not Ang II type I receptor blockers (ARBs) can prevent acute CHOP-induced cardiotoxicity.

MATERIALS AND METHODS

Study Population

In total, 52 consecutive patients with untreated non-Hodgkin lymphoma, scheduled to receive CHOP chemotherapy at our institute from February 2002 to July 2004, were asked to participate, and a total of 40 patients (ages 24–70 yrs, mean ± standard deviation [SD] of 55 ± 10 yrs; 19 males and 21 females) were enrolled. None of the enrolled patients had received any prior chemotherapy or radiation. The enrollment criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1, total serum bilirubin < 2.0 mg/dL, serum creatinine level < 2.0 mg/dL, and left ventricular ejection fraction $> 50\%$.

The study was conducted according to a protocol approved by the institutional review board at our institution. Written informed consent was obtained from each patient after the purpose of the trial, the study design, and the risks and benefits of study participation were explained.

Exclusion Criteria

The exclusion criteria included pregnancy and nursing mother. Complications including chronic or acute heart failure, other cardiac diseases (coronary artery disease, atrial arrhythmias, arrhythmia needing medication, hemodynamically significant valve disease, or hypertrophic or dilated cardiomyopathy), cirrhosis, uncontrolled diabetes mellitus, cerebral vascular accidents within the past 3 months, severe psychopathy, a contraindication for Ang II antagonists, noncompliance and treatment with any of the following drugs within the past 3 months: angiotensin-II antagonists, ACE inhibitors, vitamin E, probucol, calcium antagonists, β-blockers, or steroid pulse therapy.

CHOP Treatment for Non-Hodgkin Lymphoma

The standard CHOP chemotherapy for non-Hodgkin lymphoma consisted of doxorubicin at a dose of 50 mg/m^2, cyclophosphamide at a dose of 750 mg/m^2, vincristine at a dose of 1.4 mg/m^2 (maximum 2.0 mg/body) given intravenously on Day 1, and prednisolone at a dose of 100 mg/body daily given orally on Days 1–5.

Valsartan Treatment and Evaluation of Hemodynamic Parameters

All enrolled patients were stratified by randomization to receive, starting simultaneously with CHOP, valsartan 80 mg once daily orally or no valsartan treatment. Randomization was performed according to the minimization method.[20] We employed gender, age (< 60 yrs or ≥ 60 yrs), stage of lymphoma (Ann Arbor Stages I/II or III/ IV), and QTc dispersion at baseline (< 50 millisecond [msec] or ≥ 50 msec) as stratification factors. Oral valsartan treatment was initiated simultaneously from the first day of CHOP. If minimal side effects resulted from valsartan treatment (such as slight dizziness, palpitations, asymptomatic hypotension, and abnormal biochemical data not greater than

50% above baseline), patients were maintained at half the dose (40 mg once daily). Whenever severe adverse reactions occurred, including hypotension with clinical symptoms, renal dysfunction (serum creatinine level >2.0 mg/dL), or other abnormal biochemical data greater than 50% above baseline, valsartan treatment was immediately discontinued. We evaluated hemodynamic parameters, including systolic blood pressure, diastolic blood pressure, and heart rate before (baseline) and after valsartan treatment. Reportedly, the effects of valsartan begin approximately 2 hours after administration, and the maximum reduction in blood pressure is achieved within 6 hours.[21] Therefore, we examined blood pressure and heart rate from 5–6 hours after valsartan administration every day in each patient.

TABLE 1
Patient Profiles

Factors	ARB++ (n = 20)	ARB– (n = 20)	Total (n = 40)
Age			
< 60 yrs	15	15	30
≥ 60 yrs	5	5	10
Gender			
Male	10	9	19
Female	10	11	21
Stage of disease			
I/II	9	8	17
III/IV	11	12	23
QTc dispersion			
50 msec >	12	12	24
50 msec ≤	8	8	16

ARB: angiotensin receptor I blocker; QTc dispersion: corrected QT dispersion; msec: millisecond.

Evaluation of Acute Cardiotoxicity after CHOP

Electrocardiographic and echocardiographic studies

An electrocardiogram and an echocardiogram were performed before (baseline) and 3, 5, and 7 days after the initiation of CHOP chemotherapy. In the electrocardiographic examination, we employed corrected QT (QTc) and corrected QT dispersion (QTc dispersion) to evaluate acute cardiotoxicity. The QTc interval was measured automatically using a novel recording system (FDX-6521, Fukuda, Tokyo Japan). In brief, QT intervals were measured for 15 seconds at 25 mm/s repeated three times. QTc dispersion was automatically calculated by QT1 software (v. 1.0; Fukuda).[22] QTc and QTc dispersion were then calculated by correcting the QT interval with Bazett formula.[23] The average values from three independent measurements were employed as the QT interval, or QTc dispersion of the patient.

At time points similar to the electrocardiographic examination, echocardiographic examination was also performed for all patients using a Power Vision 6000 (Toshiba, Tokyo, Japan). The echocardiographic parameters for the study consisted of left ventricular end-diastolic diameter (LVDd) or left ventricular end-systolic diameter (LVDs), as well as systolic and diastolic function markers. As markers of systolic function, we employed left ventricular ejection fraction (LVEF) and fractional shortening (FS). To assess diastolic function, early peak flow velocity/atrial peak flow velocity (E/A), and deceleration time (DcT) were used. During the examination, the gain setting was optimized to a level just below background noise and transducer frequency was set to 2.5 or 3.5 megahertz (MHz). Cross-sectional imaging was performed in the left ventricular parasternal long axis and apical four-chamber and two-chamber views. Transmitral flow velocity patterns were recorded from the apical-long axis four-chamber view with the pulsed-wave Doppler sample volume positioned at the tips of the mitral leaflets during diastole.[24] LVEF was measured using a modified Simpson method from the apical view.[25,26] All measurements were averaged from three consecutive beats.

Natriuretic peptides measurement

Blood samples for natriuretic peptide measurement were drawn from the patients at 8:00 a.m. into chilled tubes containing aprotinin and 1 mg of ethylenediamine tetraacetic acid (EDTA)/mL and immediately placed on ice and centrifuged at 4 °C and stored at −80 °C. The samples were thawed only once, at the time of analysis. Plasma atrial natriuretic peptide (ANP) or brain natriuretic peptide (BNP) was measured with a specific immunoradiometric assay for α-human ANP or human BNP (Shionoria ANP kit; Shionogi, Tokyo, Japan). This assay system uses two monoclonal antibodies against α-human ANP or human BNP, one recognizing a carboxyterminal sequence and the other the ring structure of ANP, and measures α-human ANP or human BNP by sandwiching it between the two antibodies without extracting plasma.[27,28] The sensitivities of the ANP and BNP assays are 5 pmol/L and 2 pmol/L, respectively. The within- and between-assay coefficients of variation in each assay were all < 6.0%. All samples were measured within 1 week.

Statistical Analysis

Repeated measures analysis of variance (ANOVA) was used to compare the groups with respect to changes in neurohumoral, electrocardiographic, or echocardiographic markers before and after CHOP chemother-

TABLE 2
Change in Hemodynamic Factors in Patients Receiving Valsartan

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	*P* value
Systolic BP (mmHg)	109 ± 14	109 ± 14	107 ± 10	110 ± 12	114 ± 16	113 ± 12	110 ± 11	110 ± 14	0.28
Diastolic BP (mmHg)	65 ± 10	65 ± 9	63 ± 7	63 ± 9	66 ± 10	66 ± 12	66 ± 7	65 ± 10	0.77
Heart rate (beats/min)	79 ± 9	77 ± 9	78 ± 12	75 ± 10	75 ± 11	73 ± 9	75 ± 10	77 ± 9	0.09

BP, blood pressure.
The values are shown as the mean ± the standard deviation.
"Day" indicates the day after the initiation of chemotherapy. Valsartan treatment was initiated on the morning of Day 1.

TABLE 3
Changes in Cardiac Markers after CHOP Chemotherapy in Patients Not Receiving Valsartan

Cardiac markers	Baseline	Day 3	Day 5	Day 7	*P* value
Neurohumoral markers					
BNP (pg/mL)	19.9 ± 28.1	82.4 ± 78.9	34.4 ± 45.3	12.0 ± 18.7	< 0.0001[a]
ANP (pg/mL)	17.3 ± 15.7	39.4 ± 31.7	24.5 ± 18.8	15.0 ± 12.7	< 0.0001[a]
Echocardiographic markers					
LV end diastolic diameter (mm)	44.4 ± 5.0	49.0 ± 5.7	46.6 ± 5.9	43.6 ± 5.4	< 0.0001[a]
LV end systolic diameter (mm)	26.4 ± 6.3	26.5 ± 4.7	27.7 ± 5.2	27.0 ± 5.4	0.83
LVEF (%)	64.8 ± 5.4	68.8 ± 5.8	64.4 ± 8.3	63.7 ± 6.7	0.07
FS (%)	41.2 ± 9.3	43.2 ± 7.9	40.5 ± 7.0	38.1± 8.3	0.17
E/A	1.1 ± 0.3	1.2 ± 0.6	1.1 ± 0.3	1.0 ± 0.4	0.09
DcT (msec)	172 ± 34	182 ± 42	184 ± 35	183 ± 43	0.44
Electrocardiographic markers					
QTc interval (msec)	412 ± 17	433 ± 21	420 ± 18	418 ± 19	< 0.0001[a]
QTc dispersion (msec)	49.2 ± 9.4	58.7 ± 12.5	54.1 ± 13.4	53.8 ± 13.7	0.0005[b]

CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; BNP: brain natriuretic peptide; ANP: atrial natriuretic peptide; LV: left ventricular; LVEF: left ventricular ejection fraction; FS: fractional shortening; E/A: early peak flow velocity/atrial peak flow velocity; DcT: deceleration time; msec: millisecond; QTc interval: corrected QT interval; QTc dispersion: corrected QT dispersion.
Values are shown as the mean ± the standard deviation.
[a] $P < 0.0001$.
[b] $P < 0.001$.

apy because we had measurements for all subjects at all four times points (baseline, Days 3, 5, 7). We also used repeated measures ANOVA to evaluate changes in hemodynamic parameters before and after therapy with valsartan. A P value < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS (version 10.0; SPSS Inc., Chicago, IL).

RESULTS

Twenty of the 40 patients were randomized to the group receiving CHOP with valsartan treatment and 20 patients were randomized to the group receiving CHOP without valsartan treatment (Table 1). In only 1 of the 20 patients who received valsartan treatment did symptomatic hypotension (accompanied by dizziness and palpitations) occurred on Day 6. According to the study protocol, we discontinued valsartan treatment on Day 6 in this patient. Therefore, this patient did not complete the planned cardiac evaluations in this study. In the remaining 19 patients, there was no significant hypotension, biochemical abnormality, or renal dysfunction during the 7 days, and these 19 patients completed all planned cardiac evaluations for this study. In all patients who received valsartan treatment, systolic and diastolic blood pressures and heart rates were not found to change significantly during the 7 days of treatment ($P = 0.28$, $P = 0.77$, and $P = 0.09$, respectively) (Table 2). In addition, all 20 patients not treated with valsartan completed all planned cardiac evaluations.

In patients not treated with valsartan, after CHOP chemotherapy there were significant increases in LVDd, BNP, ANP, the QTc interval, and QTc dispersion ($P < 0.0001$, $P < 0.0001$, $P < 0.0001$, $P < 0.0001$, and $P = 0.0005$, respectively) (Table 3). Conversely, after CHOP chemotherapy there were no significant changes noted with regard to LVDs, LVEF, FS, E/A, and DcT ($P = 0.83$, $P = 0.07$, $P = 0.17$, $P = 0.09$, and $P = 0.44$, respectively) (Table 3). Furthermore, among

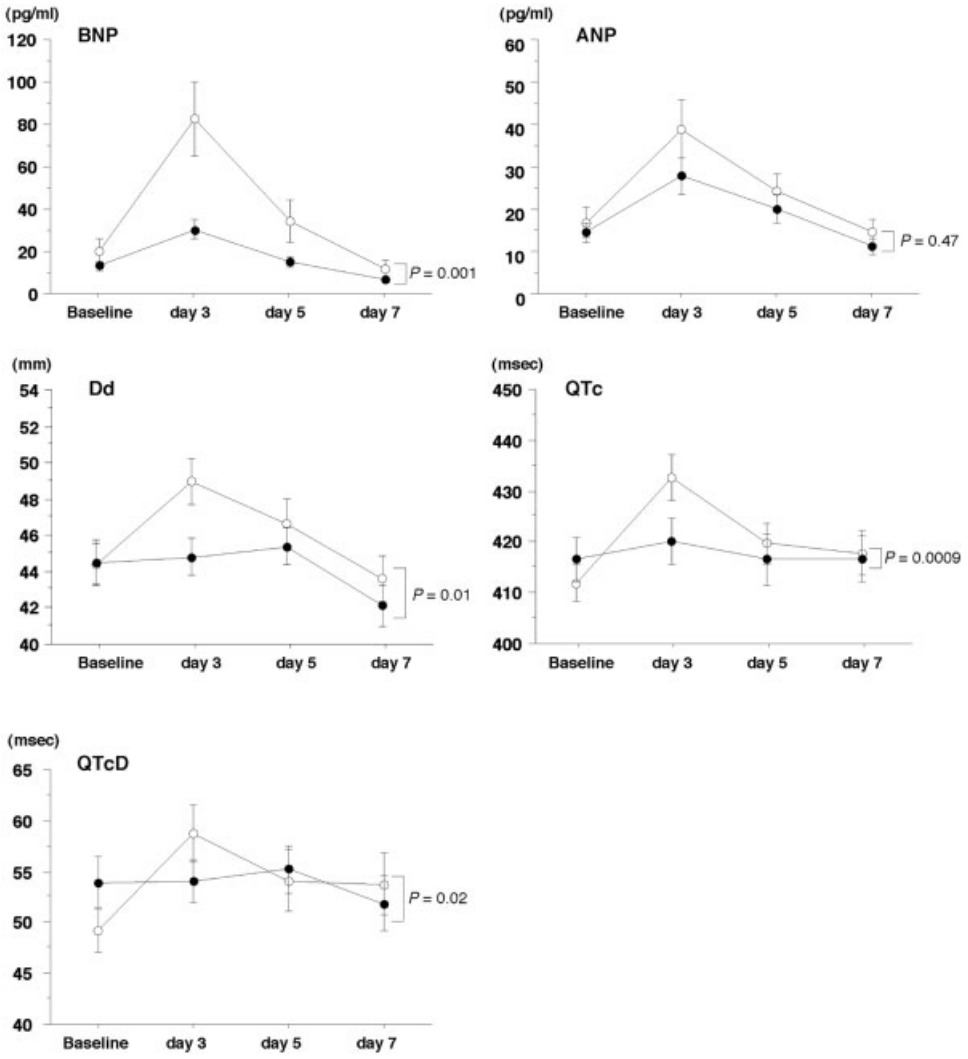

FIGURE 1. The effects of valsartan on acute cardiotoxicity after chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP). Patients with non-Hodgkin lymphoma were treated with CHOP with (closed circle) or without (open circle) 80 mg of valsartan. BNP: brain natriuretic peptide; Dd: end diastolic diameter of left ventricle; QTcD: corrected QT dispersion; ANP: atrial natriuretic peptide. Values are shown as the mean ± the standard error of the mean.

the significantly increased markers, LVDd, BNP, QTc interval, and QTc dispersion, there was a significant interaction between the group and the response of theses markers to CHOP chemotherapy over time. In other words, valsartan significantly inhibited the dilatation of LVDd ($P = 0.01$), elevation of BNP ($P = 0.001$), and prolongation of the QTc interval and QTc dispersion ($P = 0.0009$ and $P = 0.02$, respectively) after CHOP chemotherapy (Fig. 1). However, there was no significant interaction noted between the group and the response of ANP to CHOP chemotherapy over time ($P = 0.47$) (Fig. 1).

DISCUSSION

To our knowledge, the current study is the first to demonstrate that Ang II may play a critical role in acute chemotherapy-induced cardiotoxicity in humans.

First, we demonstrated that acute CHOP-induced cardiotoxicity is characterized not only by the known increase in serum ANP and BNP levels,[5,6] but also by transient changes in certain echocardiographic and electrocardiographic markers. Taken together with the fact that the significant elevation of BNP and ANP could be induced by doxorubicin alone and that no clear cardiotoxicity has been reported for other drugs used in CHOP at their doses, doxorubicin might be the predominant drug responsible for the changes in the cardiac markers observed in the present study. Transient increases in serum natriuretic peptides and LVDd might be explained as a compensative response of the heart to transient subclinical ventricular dysfunction induced by CHOP. Conversely, the significant prolongation of the QTc interval and QTc dispersion in electrocardiogram may be important, because these are known sensitive markers for chronic cardiac injury observed in ischemic and hypertensive heart disease,[29–31] as well as in anthracycline-associated car-

diac injury.[8,9,32] However, in this study, because the QTc interval and QTc dispersion returned nearly to baseline within 7 days after the initiation of CHOP chemotherapy (Fig. 1), it remains to be elucidated whether or not the changes are associated with future progression to chronic and/or late-onset cardiotoxicity. In fact, although some pathologic studies have suggested that acute cardiotoxicity may be the first manifestation of a process that ultimately leads to chronic or late-onset cardiac damage,[33,34] to our knowledge there have been no studies designed prospectively to prove this point.

When the patients were treated with valsartan together with CHOP, all the changes in cardiac markers, except for the elevation in serum ANP, were prevented, indicating that valsartan has a strong effect in preventing acute CHOP-induced cardiotoxicity. Importantly, despite valsartan-induced symptomatic hypotension in one patient, no significant change was observed in blood pressure and heart rate between the valsartan and control groups. Therefore, the beneficial effects of valsartan on acute cardiotoxicity are suggested to be mediated not indirectly by its hemodynamic effects but by the direct inhibition of Ang II, supporting previous animal experiments demonstrating a key role of the local renin–angiotensin system in doxorubicin-induced cardiac injury.[19] The inability of valsartan to prevent the elevation of ANP was not clear from the present study. However, this observation might indicate that ANP is regulated in a different manner from BNP, and most likely not directly through Ang II-type I receptors, in acute CHOP-induced cardiotoxicity. In any case, there are a series of reports suggesting that BNP is clinically of more significance than ANP for managing various types ventricular dysfunction, including that induced by chemotherapy.[5,35]

Based on the present study, the most important future question is whether the long-term administration of ARB during the entire chemotherapy can prevent chronic and/or late-onset cardiotoxicity. If possible, a number of benefits are expected in anticancer treatment, including improvement of long-term prognosis and the quality of life of cancer survivors as well as significant cost benefits. To achieve this goal, we are now promoting a multicenter, randomized trial on the long-term effects of ARB for patients undergoing repeated CHOP therapy.

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