Phase I/II Study of the Rituximab-EPOCT Regimen in Combination with Granulocyte Colony-Stimulating Factor in Patients with Relapsed or Refractory Follicular Lymphoma Including Evaluation of Its Cardiotoxicity Using B-Type Natriuretic Peptide and Troponin T Levels

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ABSTRACT

Purpose: Standard treatment for relapsed or refractory follicular lymphoma has not been established. Doxorubicin is often given during the initial treatment. The dosage or drugs chosen for salvage therapy are limited by doxorubicin-induced cardiomyopathy.

Experimental Design: The R-EPOCT (rituximab with etoposide, vincristine, pirarubicine, cyclophosphamide, and prednisone) regimen, in which less cardiotoxic pirarubicine is used instead of doxorubicin, with granulocyte colony-stimulating factor (G-CSF) was administered to 20 patients with relapsed or refractory follicular lymphoma. The safety (especially cardiotoxicity) and efficacy of this regimen were studied. As markers of cardiotoxicity, serum troponin T and plasma B-type natriuretic peptide (BNP) levels were measured.

Results: Adverse reactions occurred in 14 of the 20 patients and mainly consisted of grade 3/4 hematologic toxicity. In the evaluation of cardiotoxicity, the BNP level was slightly elevated before the treatment in two patients and the BNP level did not significantly increase after R-EPOCT treatment. The troponin T level was undetectable before and after the treatment in all patients. The response rate was 100%, with complete remission in 16 patients (80%). G-CSF administration increased both Fc γ receptor type I expression on neutrophils and antibody-dependent cellular cytotoxicity activity. There were no significant differences in the levels of Fc γ receptor type I expression nor antibody-dependent cellular cytotoxicity activity after three or five cycles of the treatment.

Conclusion: We conclude that the combination of R-EPOCT and G-CSF is well tolerated. This regimen was not cardiotoxic. We are planning a randomized trial to compare the efficacy between R-EPOCT and a combination of R-EPOCT with G-CSF.

INTRODUCTION

Advanced follicular lymphoma cannot be cured by conventional chemotherapy regimens, and more than 50% of patients die within 5 years of their first relapse. Therefore, new treatment approaches are being developed to try to improve survival and ultimately to provide a cure for patients with advanced follicular lymphoma. The EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone) therapy was developed in 1993. In this therapy, etoposide, vincristine, and doxorubicin are administered continuously for 96 hours to reduce drug resistance and cardiotoxicity (1). The complete remission (CR) rate was 8% and partial remissions (PR) rate was 73% among patients with relapsed or refractory low-grade B-cell lymphoma, with an event-free survival of 6.6 months and overall survival of 13 months. Among these patients, those who had been pretreated with doxorubicin (median, 200 mg/m²) did not develop chronic congestive heart failure. The left ventricular ejection fraction (LVEF) decreased by an average of 6.3% in patients who had been treated with zero to one course or more than six courses (2). Therefore, in patients who had previously been treated with doxorubicin, EPOCH therapy needs to be used with caution to reduce the development of latent cardiotoxicity. Pirarubicine was developed in Japan as a less cardiotoxic and highly effective antineoplastic drug (3, 4). Based on this background, we did a clinical phase I/II study of EPOCT (etoposide, vincristine, pirarubicine, cyclophosphamide, and prednisone) therapy with rituximab and granulocyte colony-stimulating factor (G-CSF) as a salvage therapy for relapsed or refractory follicular lymphoma. The purpose of this clinical phase I/II study was to evaluate the safety and efficacy of this therapy. We measured the serum troponin T level, plasma B-type natriuretic peptide (BNP) level and LVEF by echocardiogram to evaluate cardiac function. We also measured the antibody-dependent cellular cytotoxicity (ADCC) activity in neutrophils and studied the expression of cell surface antigens including Fc γ receptors type I (FcyRI; CD64) on neutrophils induced by G-CSF and rituximab.

PATIENTS AND METHODS

Study Design

This was an open-label, single-arm phase II study of the R-EPOCT regimen in combination with G-CSF for the
treatment of relapsed or refractory follicular lymphoma grade 1/2. We evaluated the response rate, cardiotoxicity (plasma BNP level, serum troponin T level, LVEF), survival period, progression-free survival, G-CSF-induced FcγR1 (CD64) expression on neutrophils, and ADCC activity of neutrophils. In addition, the safety of these regimens was investigated. This study was approved by the ethics committee of Kitasato University School of Medicine and was done in accordance with the guidelines of the Declaration of Helsinki.

Eligibility Criteria

Patients with relapsed or refractory follicular lymphoma grade 1/2 who were being treated at Kitasato University School of Medicine were enrolled. Eligible patients had histologically documented relapsed or refractory follicular lymphoma of grade 1 or grade 2 as defined by the WHO lymphoma classification (5). It was confirmed that CD20 antigen was expressed on the surface of lymphoma cells by either immunohistochemical analysis or flow cytometry using B1 or L26 anti-CD20 monoclonal antibody. Patients who were between the ages of 20 and 70 years at the time of the study with expected survival of greater than 4 months and a performance status of 0 to 2 on the Eastern Cooperative Oncology Group scale were included. Patients with stage II, III, or IV disease, as assessed by the Ann Arbor classification, were included (6). We included patients who had previously received a total dose of doxorubicin of <300 mg/m². Pretreatment laboratory examination was done within 2 weeks of study entry, and patients with the following range of laboratory results were included: absolute neutrophil count >1.5 × 10^9/L, platelets >75 × 10^9/L, creatinine <1.5 × upper limit of normal, bilirubin <2.0 × upper limit of normal, and aspartate transaminase <5 × upper limit of normal. Patients with uncontrolled infection, concomitant malignancy, unstable angina pectoris, symptomatic cardiac arrhythmia, clinical heart failure, or symptomatic pleural effusions were excluded. Pregnant or lactating women as well as patients who had clinically apparent central nervous system lymphoma were excluded from the study. All patients gave informed consent for both treatment and sample collection in accordance with institutional policy.

Treatment

Patients were treated with the EPOCT regimen plus rituximab and G-CSF. The EPOCT regimen consists of pirarubicin (10 mg/m²) as a continuous i.v. infusion on days 1 to 4; etoposide (50 mg/m²) as a continuous i.v. infusion on days 1 to 4; vincristine (0.4 mg/m²), as a continuous i.v. infusion on days 1 to 4; cyclophosphamide (750 mg/m²) i.v. on day 5; and prednisone (60 mg/m²) p.o. on days 1 to 5. The patient was administered six cycles of EPOCT once every 3 weeks. Rituximab at a dose of 375 mg/m² was administered on day −2 of cycle 3, cycle 4, cycle 5, and cycle 6. Between 30 and 60 minutes before the start of rituximab infusion, the patient was given p.o. acacetaminophen (650 mg) and diphenhydramine hydrochloride (50 mg). Corticosteroids were never given as premedication. G-CSF (2 μg/kg) was administered daily on days 10 to 21. If the nadir absolute neutrophil count was <1.5 × 10^9/L on at least three measurements, the doses of etoposide, pirarubicin, and cyclophosphamide in the present cycle were reduced by 20% compared with the respective dose in the previous cycle. If the nadir platelet count was <25 × 10^9/L, the doses of etoposide, pirarubicin, and cyclophosphamide in the present cycle were reduced by 20% compared with the respective dose in the previous cycle.

Response Criteria

The tumor response was assessed after the six cycles of treatment or at the end of treatment. Disease assessment included the following evaluations: physical examination and assessment of performance status and B symptoms (baseline, at weeks 6, 12, and 18, and every 3 months through 2 years), chest X-ray (baseline), bone marrow aspiration and biopsy (baseline, and to confirm a CR if the patient was positive at baseline), and computed tomography or magnetic resonance imaging (baseline, at weeks 6, 12 and 18, and every 3 months through 2 years). The tumor responses were classified as CR, PR, stable disease, or progressive disease according to the International Workshop for non-Hodgkin’s lymphoma response criteria (7). These classifications were defined as follows: CR, the disappearance of all lesions and of radiologic (<1.5 cm) or biological abnormalities observed at diagnosis and the absence of new lesions; CRu, presence of lymph node/mass greater than 1.5 cm that has regressed by more than 75% and is gallium negative; PR, regression of all measurable lesions by more than 50%, the disappearance of nonmeasurable lesions, and the absence of new lesions; stable disease, regression of measurable lesions by ≤50%, or no change in the nonmeasurable lesions, and no growth of existing lesions or no appearance of new lesions; progressive disease, the appearance of new lesions, growth of the initial lesions by >25%, or growth of measurable lesions that had regressed during treatment but that subsequently grew by >50% of their smallest dimensions.

Troponin T and BNP Assays

For determination of the serum troponin T level, the blood sample was centrifuged at 1000 × g at 4°C for 15 minutes and stored at −70°C until assayed. The third-generation Enzymun test troponin T assay was used, which had been developed based on a prototype of the new electrochemiluminescence-based Elecsys system (Roche Diagnostics, Tokyo, Japan). The lower limit of detection of troponin T was 0.01 μg/mL. For determination of the plasma BNP level, blood samples were collected in chilled tubes containing EDTA, disodium salt, and aprotinin (500 IU/mL). The plasma was separated by centrifugation at 1000 × g at 4°C for 15 minutes and then stored at −70°C until analysis. The BNP concentration was measured by a commercial RIA kit for human BNP (Shiono RIA BNP assay; Shionogi Co., Ltd, Tokyo, Japan). The lower limit of detection and the upper limit of the reference interval of the BNP assay were 0.2 and 20 pg/mL, respectively (8). The blood sample was after the third cycle of treatment obtained immediately after the third cycle of treatment was completed.

ADCC Assay

The ADCC assay was done as described previously (9). In brief, target cells (chicken red blood cells) were labeled with 51Cr (100 μCi per 10⁶ cells) at 37°C for 1 hour. Cells were
washed thrice and resuspended in culture medium at a concentration of 5 × 10^6 cells/mL. Cells were then sensitized with antibodies (final concentration, 5 μg/mL). The neutrophils of a patient and target cells were added to 96-well, flat-bottom microtiter plates at an E:T ratio of 10:1 and adjusted to a final volume of 200 μL. The plates were centrifuged at 200 × g for 1 minute and incubated at 37°C under 5% CO2 for 20 hours. 51Cr release was measured in triplicate and expressed as counts per minute (cpm). The percentage of specific lysis was calculated using the following formula: % specific lysis = (experimental release – spontaneous cpm)/(maximal cpm – spontaneous cpm) × 100. The maximal 51Cr release was determined by adding saponin (5% m/v, 100 μL) to target cells, and spontaneous 51Cr release was determined by measuring 51Cr release from unsensitized target cells in the absence of effector cells. ADCC experiments were done in duplicate.

**Immunophenotyping**

After the neutrophils were washed once in PBS and resuspended in PBS containing 1% bovine serum albumin (w/v), immunophenotyping was done as previously described (10), using phycoerythrin R–conjugated monoclonal antibodies directed against CD20, CD64 (FcγRI), or CD89 (Fcα RI; Beckman-Coulter, Hialeah, FL). An irrelevant isotype-matched control monoclonal antibody was used in all experiments. Flow cytometry was carried out using a FACSscan (Becton Dickinson, San Jose, CA). The mean fluorescence intensity was measured by flow cytometry, and all data were corrected for the mean fluorescence intensity in the presence of the irrelevant control antibody.

**Statistical Analyses**

All statistical analyses were done with SAS software (version 6.10, SAS Institute, Cary, NC). Data are expressed as mean ± SD unless otherwise indicated. The serum troponin T levels or plasma BNP levels at different time points were compared using the Wilcoxon signed rank test. The duration of the response and survival were assessed using the method of Kaplan and Meier (11). A P < 0.05 was considered significant.

**RESULTS**

**Patient Characteristics**

The clinical characteristics of the 20 patients with relapsed or refractory follicular lymphoma in this study are shown in Table 1. There were 12 males and 8 females with a median age of 57 years (range, 42-69 years). The histologic subtype was follicular lymphoma grade 1 in 7 patients and follicular lymphoma grade 2 in 13 patients. Two patients had stage II disease, 9 patients had stage III disease, and 9 patients had stage IV disease. There were 18 relapsed patients and 2 patients who were resistant to the initial treatment. Twelve patients had previously undergone chemotherapy regimen and 8 patients had previously undergone two chemotherapy regimens. The total dose of doxorubicin that had been administered in the previous chemotherapy regimens was 250 mg/m² (median; range, 250-300 mg/m²).

**Adverse Drug Reactions**

We assessed the toxicity of the EPOCT regimen plus rituximab over 120 cycles administered to 20 patients (Table 2). Neutrophil toxicity of grades 3 to 4 was found in 98 cycles (82%). Among the 7 patients with neutropenia of grade 4, 4 patients developed an uncomplicated fever following G-CSF treatment. The other 3 patients did not develop fever after G-CSF administration only. Five patients developed grade 3 thrombocytopenia and they required platelet transfusion. Nine of the 15 patients who developed grade 3 to 4 hematologic toxicities showed bone marrow infiltration of lymphoma cells. Infusion-related adverse events after rituximab treatment were found in 23 cycles (19%). The four most frequently observed adverse events following rituximab treatment were fever, chills/rigor, rash, and headache. Infusion-related adverse events typically occurred 1 to 2 hours after the start of infusion. The majority of the infusion-related adverse events were classified as mild to moderate (toxicity grade 1 or 2) and occurred during the first infusion. They were effectively managed with prophylactic or supportive antihistamines and antipyretics, and resolved within 24 hours. Nonhematologic toxicities were mainly gastrointestinal, neurologic, and hepatic disorders. There were no deaths associated with the treatment.

**Serum Troponin T and Plasma BNP Levels**

Troponin T is a protein that forms troponin complexes on thin filaments of skeletal muscles and is involved in the control of muscle contractions. The troponin T level is considered to be the most specific marker of myocardial damage. Troponin T is a structural protein of the myocardium; however, it also exists in the cytoplasm of myocardial cells. Therefore, the serum troponin T level continues to be significantly elevated from the time of early myocardial damage (after 3-6 hours) up through 2 to 3 weeks after the cardiac event (12). BNP, which is mainly secreted by the ventricles, has vasodilating and uretic effects, and it plays an important role in controlling body fluid volume and blood pressure. The plasma BNP level begins to increase in patients with asymptomatic cardiac failure and it increases markedly according to the severity of the cardiac failure. Therefore, the plasma BNP level is important for assessing cardiac dysfunction (13). In this study, we evaluated the cardiotoxicity of pirarubicine with these two markers and the LVEF by echocardiogram. The troponin T and BNP levels were measured before treatment, after two cycles of the treatment, after four cycles of treatment, and 1 month after completion of treatment. Serum troponin T was undetectable in all patients before the start of treatment, and it remained undetectable during and after the treatment in all patients. The BNP level was

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y), (range)</td>
<td>57 (42-69)</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>12/8</td>
</tr>
<tr>
<td>Histology, follicular lymphoma G1/G2</td>
<td>7/13</td>
</tr>
<tr>
<td>Stage II/III/IV</td>
<td>2/9/9</td>
</tr>
<tr>
<td>LDH (normal/elevated)</td>
<td>12/8</td>
</tr>
<tr>
<td>Disease status</td>
<td>18</td>
</tr>
<tr>
<td>Relapsed</td>
<td>18</td>
</tr>
<tr>
<td>Primary refractory</td>
<td>2</td>
</tr>
<tr>
<td>No. of prior chemotherapy regimens</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Total dose of doxorubicin median (range), mg/m²</td>
<td>250 (200-300)</td>
</tr>
</tbody>
</table>

Abbreviation: LDH, lactate dehydrogenase.
slightly elevated in two patients before the treatment (22.4 and 25.6 pg/mL; normal, <20 pg/mL). After four cycles of treatment, the BNP level in these two patients increased to 26.8 and 28.8 pg/mL, respectively, but it returned to approximately the previous level one month after completion of treatment (Fig. 1). These two patients showed no abnormalities on ECG and echocardiogram. No patient had a reduction in LVEF of more than 5% at any time during or after the treatment. These findings suggest that the addition of pirarubicine to the treatment regimen did not increase its cardiotoxicity.

Analysis of CD64 Expression on Neutrophils and ADCC Activity upon G-CSF Administration

The rationale of adding G-CSF to the treatment regimen containing rituximab was to induce the expression of FcγRI on the circulating neutrophils, while at the same time increasing the number of neutrophils. We evaluated the level of ADCC activity of G-CSF-stimulated neutrophils and the expression of Fc receptors on neutrophils obtained from all 20 subjects. The neutrophils that were used for analysis of ADCC activity were obtained at the same time as the neutrophils used for analysis of expression of Fc receptors. As shown in Fig. 2A, upon G-CSF administration during the second cycle of treatment, the level of FcγR1 (CD64) expression on neutrophils increased from 60.1 ± 3.6 (mean fluorescence intensity) before G-CSF administration (day 1) to 324.7 ± 33.2 (P = 0.0005) after 9 days of administration of 2 μg/kg G-CSF (day 18; data not shown). After 11 days of G-CSF administration (day 20), the level of FcγR1 (CD64) expression was 346.2 ± 24.2. The change in the neutrophil count and induction of FcγRI expression by G-CSF showed similar patterns during the second cycle and during the fourth cycle of treatment. The expression of FcαRI (CD89) on neutrophils was examined in a similar fashion. There was no remarkable change in the level of FcαRI expression before and after G-CSF administration. During the second cycle of treatment, the level of ADCC activity significantly increased from 20.2 ± 4.2% before G-CSF administration (day 1) to 68.6 ± 4.4% at 9 days after the start of administration of 2 μg/kg G-CSF (day 18; data not shown; P = 0.0002). A similar pattern was seen during the fourth cycle of treatment (Fig. 2B). Thus, it was confirmed that G-CSF increased FcγRI (CD64) expression on neutrophils and ADCC activity.

**Response to the R-EPOCT Regimen**

As shown in Table 3, the overall response rate to the R-CHOP (cyclophosphamide-Adriamycin-vincristine-prednisone) regimen with or without G-CSF was 100%; CR, 16 patients, 80% [including CR (unconfirmed), 6 patients, 30%]; PR, 4 patients, 20%. Nine patients were positive for bcl-2 gene rearrangement in peripheral blood cells and/or bone marrow cells before the treatment. After the treatment, 8 patients achieved molecular remission. Fifteen (83.3%) of the 18 relapsed patients and 1 (50%) of the 2 primary refractory patients achieved CR. The median length of the observation period was 19 months, and 4 of the 20 patients relapsed. The 2-year survival rate was 92.1%.

**DISCUSSION**

The clinical introduction of rituximab has dramatically changed the treatment strategy for follicular lymphoma. The improvement in time to progression with rituximab-combined

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**Table 2 Adverse drug reactions**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
<th>No. of cycles</th>
<th>Percentage of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>20</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions (≥ grade 2)</td>
<td>23</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil (grade 3/4)</td>
<td>98</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Platelet (grade 3)</td>
<td>24</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Nonhematologic toxicity (≥ grade 2)</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>16</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 1** Changes in the plasma BNP levels before the EPOCT regimen treatment, after two cycles of treatment, after four cycles of treatment, and 1 month after completion of treatment (After). The plasma BNP level was above the reference range (normal, <20 pg/mL) before the treatment in 2 of the 20 patients and it increased during the fourth cycle of treatment in both patients, but it returned to nearly the previous level 1 month after completion of treatment.
chemotherapy has been reported (14). Relapsed cases are often resistant to doxorubicin; therefore, when the total dose of doxorubicin is taken into consideration, the development of cardiotoxicity by salvage therapy is worrisome. Recently, several studies reported that the cytotoxic effect of rituximab is increased by combination with various cytokines (15–17). It has been suggested that the treatment effect of rituximab is increased by combination with G-CSF because G-CSF increases the cytotoxicity of neutrophils through ADCC (18). We previously reported that when the R-CHOP regimen was combined with G-CSF, G-CSF increased FcγR1 (CD64) expression on neutrophils and ADCC activity. Because there were no significant differences in the degree of increase of CD64 expression and ADCC activity between those who had been treated with 2 or 5 μg/kg of G-CSF, we reported that the optimal dose of G-CSF when combined with the R-CHOP regimen was 2 μg/kg (19). In the present study on the R-EPOCT regimen, G-CSF at 2 μg/kg was administered from 11 days before rituximab administration to 1 day after rituximab administration as a rule. The results showed that FcγR1 (CD64) expression and ADCC activity were significantly higher after administration of G-CSF compared with the respective level before G-CSF administration. As for the treatment effect, the results were similar to those obtained in previous studies on combination chemotherapy with rituximab: the CR in the present study was 80% and the PR was 20%. The rate of remission was higher among the relapsed patients than among the refractory patients. However, the 2-year progression-free survival was 76.6% and the treatment method needs to be evaluated further, including maintenance therapy with rituximab. As for adverse drug reactions, hematologic toxicity was the main adverse reaction. It should be particularly noted that no treatment-related deaths occurred and the treatment seemed to be safe. The clinical use of doxorubicin and combination chemotherapy including pirarubicine on elderly patients with untreated non-Hodgkin’s lymphoma and compared the cardiotoxicity of the two treatments. The results showed that the cardiac toxicity of doxorubicin was manifested as cardiac sympathetic dysfunction and cardiac mitochondrial damage when the total dose reached ≥250 to 300 mg/m², and a LVEF of <50% became more common when the total dose exceeded 350 mg/m². Cardiac sympathetic dysfunction caused by pirarubicine was detected at a total dose of ≥400 mg/m², and cardiac mitochondrial damage was observed at doses of ≥300 to 350 mg/m². Therefore, it seems that pirarubicine can be safely used at a dose that is 50 to 100 mg/m² higher than the dose of doxorubicin (4). Generally, determination of LVEF by echocardiography or radionuclide ventriculography to detect doxorubicin-induced cardiomyopathy is widely used. However, these methods have limitations in the early detection of cardiotoxicity. Recently, the usefulness of the BNP and troponin T levels as biomarkers of doxorubicin-induced cardiomyopathy in rats has been reported (20). The serum BNP level is elevated not only in patients with severe chronic congestive heart failure but also in patients with asymptomatic cardiomyopathy. Therefore, it may be possible to detect the early stage of doxorubicin-induced cardiomyopathy by measuring BNP and troponin T levels.

**Table 3: Results of treatment**

<table>
<thead>
<tr>
<th>Response</th>
<th></th>
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<tbody>
<tr>
<td>CR</td>
<td>16 (80)</td>
</tr>
<tr>
<td>CR unconfirmed</td>
<td>6 (30)</td>
</tr>
<tr>
<td>PR</td>
<td>4 (20)</td>
</tr>
<tr>
<td>bel-2 gene rearrangement, positive</td>
<td>9/20 (45)</td>
</tr>
</tbody>
</table>

**Molecular response**

| Peripheral blood cells | 8/9 (88.9) |
| Bone marrow cells     | 8/9 (88.9) |

**Disease status**

| Relapsed CR | 15/18 (83.3) |
| Primary refractory | 1/2 (50) |

**Survival percentage (median follow-up, 19 mo)**

| Overall survival (2 y) | 92.1 |
| Progression-free survival (2 y) | 76.6 |

**NOTE.** Values in parentheses are percentages.
left ventricular dysfunction and it is useful as a marker of left ventricular dysfunction in patients who had received anthracycline therapy (21). The troponin T level is a prognostic factor for acute coronary syndrome and it has recently been used for early detection of doxorubicin-induced cardiomyopathy (22). Koh et al. (20) reported that there were significant correlations between the decrease in percent fractional shortening of the left ventricle and the increase in serum BNP level or plasma troponin T level, and the troponin T level was highly sensitive in detecting doxorubicin-induced cardiomyopathy. In our study, the serum troponin T level was normal, that is, below the detection limit, in all patients before and after treatment, and the plasma BNP level was slightly elevated in two patients before treatment, but 1 month after completion of treatment the levels returned to nearly the previous values. There were no abnormalities in LVEF or percent fractional shortening by echocardiogram before and after treatment in all patients. Therefore, pirarubicine was not cardiotoxic nor did it increase the cardiotoxicity of the other drugs in our chemotherapy regimen. In conclusion, R-EPOCT with G-CSF was safe for the treatment of relapsed or refractory follicular lymphoma. In addition, R-EPOCT with G-CSF could be administered to patients who had previously been treated with doxorubicin without worsening cardiotoxicity by pirarubicine. We are planning to carry out a randomized controlled trial of R-EPOCT with G-CSF and R-EPOCT in the future.

REFERENCES

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