Table 2. *(Cont'd)*

Factor	Before		After	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Diagnosis				
ALL	1.00		1.00	
AML	0.86 (0.69-1.07)	.18	0.88 (0.70-1.09)	.24
CML	0.82 (0.66-1.01)	.063	0.84 (0.68-1.04)	.11
MDS	1.24 (0.93-1.66)	.13	1.30 (0.98-1.74)	.070
Regimen				
Cy-TBI			1.00	
Cy-TBI$^+$			1.45 (1.20-1.74)	<.0001
Bu-Cy			1.31 (1.00-1.73)	.050
Bu-Cy-TLI			1.43 (0.91-2.26)	.12

Acute and Chronic GVHD

The incidence of grade II to IV and grade III/IV acute GVHD was 43.9% and 16.7%, respectively. Male sex, higher donor age, HLA mismatch in the GVH direction, ABO minor mismatch, underlying disease, high-risk disease, and the GVHD prophylaxis regimen affected the incidence of grade III/IV acute GVHD with at least borderline significance ($P < .10$). Among these, HLA-allele mismatch in the GVH direction, ABO minor mismatch, underlying disease, and GVHD prophylaxis were identified as independent risk factors by a multivariate analysis (Table 2). There was no difference in the incidence of acute GVHD among the 4 types of conditioning regimens after adjustment for these risk factors (Table 2 and Figure 1B).

Chronic GVHD was observed in 49.7% of patients who achieved engraftment and survived disease free for at least 100 days after transplantation. Only the presence of an HLA-allele mismatch in the GVH direction significantly affected the incidence of chronic GVHD by multivariate analysis. The type of conditioning did not significantly affect the incidence of chronic GVHD.

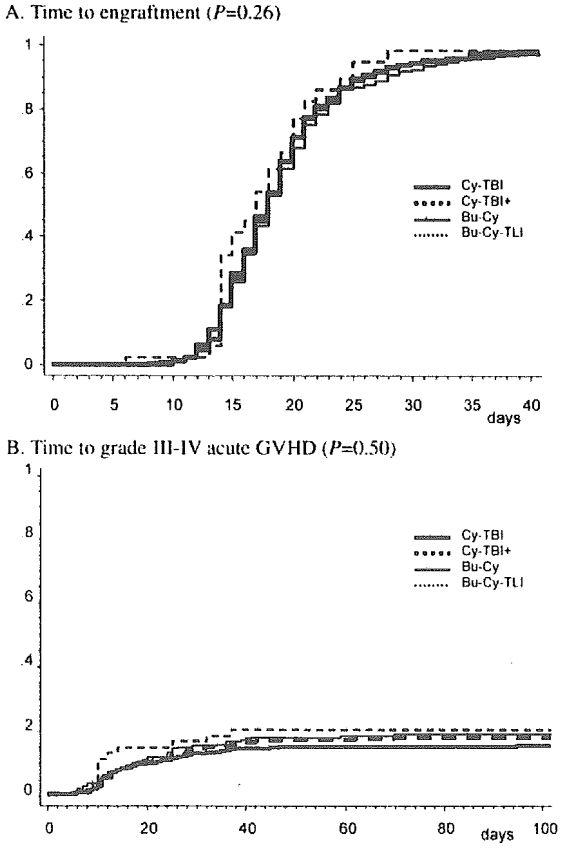

Figure 1. Days to engraftment (A) and days to grade III/IV acute GVHD (B) grouped according to the type of conditioning regimen.

Survival after Transplantation

Overall survival and disease-free survival at 5 years after transplantation for all of the patients was 46.2% and 42.5%, respectively. Overall survival stratified by disease status, grouped according to the conditioning regimen, is shown in Figure 2. A significant difference in survival was observed in standard-risk patients. Risk factors for shorter survival with a *P* value of <.10 identified by the log-rank test included male sex, higher recipient age, higher donor age, HLA mismatch in both the GVH and HVG directions, ABO major mismatch, high-risk disease, cytomegalovirus seropositivity, use of G-CSF after transplantation, and GVHD prophylaxis consisting of cyclosporin A and methotrexate. Proportional hazard modeling identified 6 independent significant risk factors: higher patient age, higher donor age, HLA-allele mismatch in the GVH direction, use of G-CSF, high-risk disease, and the use of the combination of cyclosporin A and methotrexate (Table 2). When we added the type of conditioning regimen to the proportional hazard model, the Cy-TBI$^+$ and Bu-Cy regimens were significantly inferior to the Cy-TBI regimen (relative risk [RR], 1.45; 95% CI, 1.20-1.74; $P < .0001$ and RR, 1.31; 95% CI, 1.00-1.73; $P = .050$, respectively).

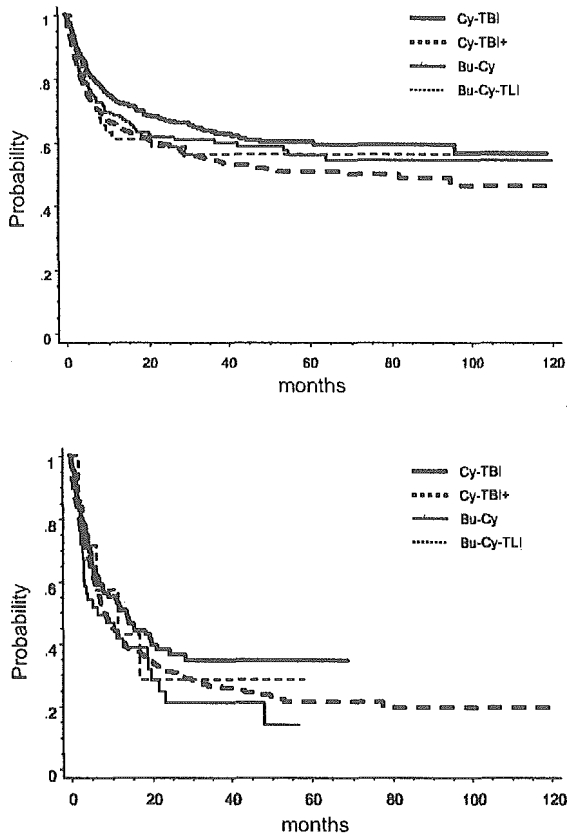

Figure 2. Overall survival grouped according to the type of conditioning regimen in standard-risk (A) and high-risk (B) patients.

Analyses Based on Detailed HLA Matching

We added analyses based on detailed HLA matching because it has been reported that the outcome of unrelated BMT is affected not only by the presence of HLA-allele mismatch, but also by whether the HLA-allele mismatch belongs to class I or class II [16,18]. In this study, none of the HLA-A/-B antigen, HLA-C antigen, HLA-DR antigen, HLA-A/-B allele, HLA-C allele, or HLA-DRB1 allele mismatches in the HVG direction significantly affected the incidence of engraftment failure, probably because of the small number of patients in each group. However, mismatches in the GVH direction at the HLA-A/-B antigen, HLA-C antigen, HLA-A/-B allele, HLA-C allele, and HLA-DRB1 allele significantly affected the incidence of grade III/IV acute GVHD in univariate analyses. These factors were included in the multivariate analysis, and HLA-A/-B allele, HLA-C allele, and HLA-DRB1 allele mismatches were shown to be independently significant. However, the effect of the conditioning regimen on the incidence of grade III/IV acute GVHD was not significant after adjustment for the independent significant factors. As for survival after transplantation, mismatches in both the HVG and GVH directions at the HLA-A/-B antigen, HLA-C antigen, HLA-A/-B allele, HLA-C allele, and HLA-DRB1 allele significantly affected overall survival in univariate analyses. Among these, the presence of an HLA-A/-B antigen mismatch in the HVG direction and an HLA-A/-B allele mismatch in the GVH direction were identified as independent significant risk factors for overall survival. After adjustment for these factors, as well as other independent significant risk factors, the adverse effects of the Cy-TBI$^+$ and Bu-Cy regimens remained significant (RR, 1.42; 95% CI, 1.18-1.70; $P = .0002$ and RR, 1.31; 95% CI, 1.00-1.72; $P = .052$, respectively).

Other Statistical Analyses to Ensure the Results

We added statistical analyses to ensure the findings of this study. First, we repeated the analyses by using only patients who received the Cy-TBI or Bu-Cy regimen, to confirm the difference between the 2 regimens. The findings were almost the same, and the use of Bu-Cy adversely affected the incidence of engraftment failure and overall survival (OR, 2.53; 95% CI, 1.00-6.39; $P = .049$ and RR, 1.32; 95% CI, 1.00-1.75; $P = .053$, respectively).

Next, we changed the method of the multivariate analyses to include all factors with at least borderline significance ($P < .10$) in univariate analyses, as well as the underlying disease and the type of conditioning regimen, followed by a stepwise deletion of nonsignificant factors. This change in the statistical method did not change the major findings of this study. The Bu-Cy regimen was inferior to the Cy-TBI regimen in the incidence of engraftment failure and overall survival (OR, 2.49; 95% CI, 1.02-6.12; $P = .045$ and RR, 1.33; 95% CI, 1.02-1.75; $P = .046$, respectively). The Cy-TBI$^+$ regimen was inferior to the Cy-TBI regimen in overall survival (RR, 1.46; 95% CI, 1.21-1.75; $P < .0001$).

Relapse and Nonrelapse Mortality

To evaluate the cause of the difference in survival among the different types of conditioning regimens, we further analyzed the incidences of relapse and nonrelapse mortality. Multivariate analyses revealed that the incidence of relapse after the Bu-Cy-TLI regimen was significantly lower than that after the Cy-TBI regimen (RR, 0.13; 95% CI, 0.02-0.90; $P = .039$, adjusted for ABO major mismatch, underlying disease, disease status, and GVHD prophylaxis), although this benefit was offset by a significant increase in the incidence of nonrelapse mortality (RR, 1.89; 95% CI, 1.20-3.00; $P = .0061$, adjusted for recipient age, donor age, underlying disease, disease status, HLA-allele mismatch in the HVG direction, G-CSF, and GVHD prophylaxis); this resulted in similar survival. The incidence of nonrelapse mortality after the Cy-TBI$^+$ regimen was significantly higher than that after the Cy-TBI regimen (RR, 1.48; 95% CI, 1.20-

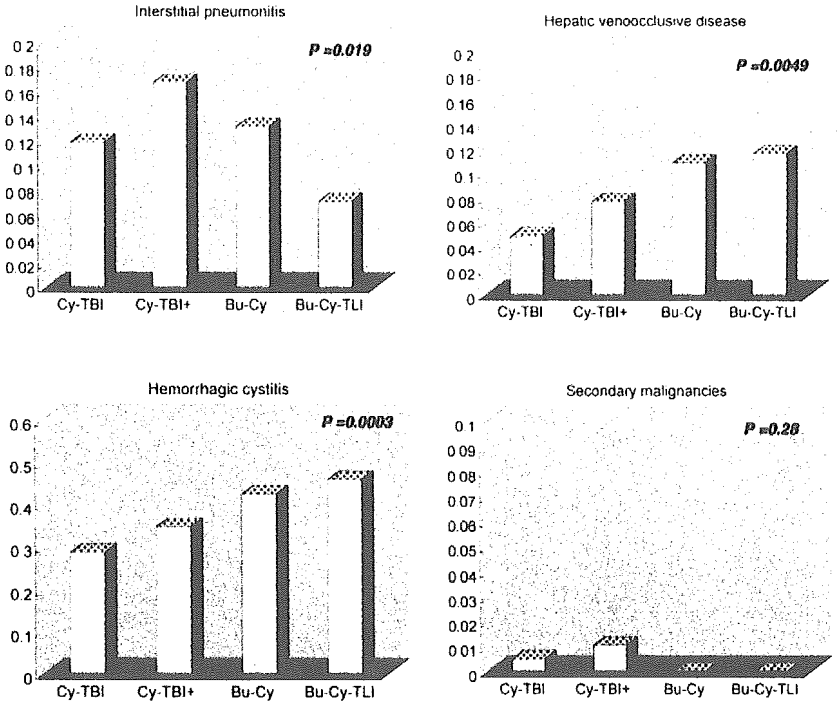

Figure 3. Incidence of interstitial pneumonitis, hepatic veno-occlusive disease, and secondary malignancies, excluding posttransplantation lymphoproliferative disorders.

1.84; P = .0003, adjusted as described previously), whereas there was no difference in the incidence of relapse (RR, 0.84; 95% CI, 0.64-1.11; P = .22). There was no significant difference in the incidence of relapse and nonrelapse mortality between the Cy-TBI and Bu-Cy regimens (RR, 0.89; 95% CI, 0.57-1.38; P = .59 and RR, 1.21; 95% CI, 0.89-1.65; P = .23, respectively).

Other Complications after Transplantation

The incidence of interstitial pneumonitis was significantly different among the 4 conditioning regimens (P = .019; Figure 3). The incidence of interstitial pneumonitis after the Cy-TBI$^+$ regimen was significantly higher than that after the Cy-TBI regimen (OR, 1.59; 95% CI, 1.13-2.23; P = .0076, adjusted for underlying disease, HLA-allele mismatch in the HVG direction, and GVHD prophylaxis). A statistically significant difference was not observed between the Cy-TBI and Bu-Cy regimens (P = .66). The incidence of VOD was also significantly different among the 4 conditioning groups (P = .0049). It was significantly higher after the Cy-TBI$^+$, Bu-Cy, and Bu-Cy-TLI regimens than after the Cy-TBI regimen (OR, 1.64; 95% CI, 1.00-2.71; P = .052; OR, 3.00; 95% CI, 1.62-5.45; P = .0005; and OR, 3.20; 95% CI, 1.11-8.24; P = .032, respectively, adjusted for underlying disease, HLA-allele mismatch in the HVG direction, ABO major mismatch, ABO minor mismatch, and G-CSF). The incidence of hemorrhagic cystitis was significantly affected by the type of conditioning regimen (P = .0003). It was also significantly higher after the Cy-TBI$^+$, Bu-Cy, and Bu-Cy-TLI regimens than after the Cy-TBI regimen (OR, 1.37; 95% CI, 1.09-1.72; P = .0075; OR, 1.85; 95% CI, 1.34-2.56; P = .0002; and OR, 2.11; 95% CI, 1.16-3.85; P = .015, respectively, adjusted for underlying disease and donor sex).

Secondary malignancies excluding posttransplantation lymphoproliferative disorders developed in 8 patients a median of 35 months (range, 15-84 months) after transplantation, including MDS in 2 and AML, thyroid cancer, uterine body cancer, esophageal cancer, breast cancer, and squamous cell cancer in 1 each. The incidence of secondary malignancies was not significantly different among the 4 conditioning groups.

DISCUSSION

In this study, we retrospectively evaluated the effect of the conditioning regimen on the outcome of unrelated BMT. The Cy-TBI regimen was superior to the Bu-Cy regimen, not only with regard to the incidence of engraftment failure, but also for overall survival after transplantation. The addition of TLI to the Bu-Cy regimen decreased the incidences of engraftment failure and relapse but increased nonrelapse mortality. Intensified conditioning regimens in which

another antineoplastic agent was added to the Cy-TBI regimen resulted in increased nonrelapse mortality and inferior survival.

On the basis of the results of randomized controlled trials and their meta-analysis, the Cy-TBI regimen is generally preferred to the Bu-Cy regimen except for patients with CML in chronic phase in HSCT from an HLA-identical sibling donor [5-10]. This study showed that Cy-TBI may be the first-choice regimen in most patients who undergo unrelated BMT unless the patient has a condition that precludes the use of TBI, such as previous high-dose irradiation to a major organ. The weakness of the Bu-Cy regimen was apparent in the increased incidences of engraftment failure and VOD. As a current general practice in Japan, Bu is administered orally without monitoring the plasma concentration. Therefore, the use of intravenous Bu or oral Bu targeted to a predetermined plasma level may improve the outcome after the Bu-Cy regimen [22]. However, further trials are required to evaluate the efficacy of intravenous Bu and targeted oral Bu.

Higher nonrelapse mortality after the intensified Cy-TBI^{+} regimen might reflect the possibility that the regimen was preferentially used in patients with advanced diseases. However, the incidence of nonrelapse mortality was significantly higher after adjustment for disease status and also when the comparison was limited to patients with standard-risk disease (RR, 1.47; 95% CI, 1.14-1.90; P = .0031). Conversely, a decrease in the relapse incidence was not observed either in standard-risk or in high-risk patients (RR, 0.81; 95% CI, 0.57-1.15; P = .24 and RR, 0.89; 95% CI, 0.57-1.39; P = .60). Therefore, these results did not show any benefit for the intensified regimens.

This was a retrospective study, and it was impossible to completely eradicate biases. First, non-TBI regimens were preferentially used in older patients. Second, the use of Bu-based regimens was less frequent in ALL compared with myeloid malignancies. Third, the intensified Cy-TBI^{+} regimen was most frequently used in young patients with high-risk diseases. Therefore, we adjusted the effect of the conditioning regimen for these variables in multivariate analyses. We should also consider the "center" effect as a possible bias. However, a study from the Japan Society for HSCT did not show a significant center effect in unrelated BMT in Japan [23]. The inclusion of patients who underwent transplantation from 1993 and 2002 might have resulted in the significant variations in transplantation procedures. We could not obtain detailed information of supportive care, and this is one of the limitations of this type of registry data study.

The use of G-CSF after transplantation significantly adversely affected survival. A similar result was observed in a retrospective study by the European Group for Blood and Marrow Transplantation [24]. However, such an adverse effect has not been shown in prospective randomized controlled trials that evaluated the use of G-CSF after transplantation [25]. Patients with preexisting infections or other comorbidities might have tended to receive G-CSF. These data were not included in the analyses and thus might have biased the results.

Although a definite conclusion cannot be made without a randomized controlled trial, >1000 patients will be required to detect the meaningful difference (RR, 1.31) in survival between the Cy-TBI and Bu-Cy groups that was seen in this study at a statistically significant level with α and β errors of 5% and 20%, respectively. Thus, realistically, this retrospective study that considered possible biases in multivariate analyses may be the best evidence. More than 30 years have passed since the introduction of the Cy-TBI regimen. Nevertheless, the Cy-TBI regimen still seems to be the most suitable regimen not only in HSCT from an HLA-identical sibling donor, but also in unrelated BMT.

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気道上皮細胞に対する好酸球顆粒蛋白および Respiratory Syncytial ウイルスの傷害性

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原　著

気道上皮細胞に対する好酸球顆粒蛋白および Respiratory Syncytial ウイルスの傷害性

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The Toxicity of Eosinophil Granule Proteins and Respiratory Syncytial Virus in Airway Epithelium Cells

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Abstract

Eosinophils are one of the inflammatory cells involving allergic diseases and are recognized as effector cells in airway inflammation of bronchial asthma. The two major effector functions are the release of toxic granule proteins and active oxygen species. Here we examined the effects of toxic granule proteins of human eosinophils, such as major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN) against airway lung carcinoma cells (A549 cell, ATCC CCL-185) which were infected with respiratory syncytial virus (RSV). Cytopathic effects of A549 cells were observed in the course of time (every 24 hour). None of injury on A549 cells was observed in cases of RSV alone whose dose was 0.1 and 1 moi up to 48 hours. High concentrations of MBP and EPO did harm to A549 cells by themselves after 24 hours, however ECP and EDN didn't such response even after 48 hours in macro phase. On the other hand, in case of infection with RSV, the degree of injury in A549 cells treated with MBP and EPO was significantly increased; it depended on the concentration of RSV in macro phase. The viability of A549 cells which were infected and/or treated were also measured by the cell viability analyzer (Vi-CELL). It exhibited that the viability of A549 cells which were infected with RSV and following treated with eosinophil granule proteins was lower than that of RSV infection alone. The results suggested that eosinophils and its products might induce excess injury to airway epithelial cells especially when airway epithelial cells were infected with RSV and this might promote the eosinophilic inflammation in bronchial asthma.

Key words: major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), A549 cell

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はじめに

感染症の重症化には，病原体側の要因のみならず宿主側の免疫反応が複雑に関与することが推定されている。例えばRespiratory Syncytial ウイルス（RSV）や

ライノウイルスなどによる呼吸器ウイルス感染症は気道過敏症の亢進を来すことから，気管支喘息の発症あるいは増悪を引き起こすことが知られている[1, 13]。

一方，好酸球は遅発型気道過敏症の病態に深く関与する主たる炎症性細胞であり，その機能の中でも，活性酸素の生成，細胞外へ放出されるmajor basic protein (MBP)，およびeosinophil peroxidase (EPO) などの顆粒蛋白は炎症反応の増悪因子として知られている[5, 10]。しかしながら，呼吸器ウイルス感染症と好酸球が互いに関連して引き起こす過剰な免疫反応については不明な点が多い。

そこで今回，特に喘息の発症と増悪に関与していると考えられているRSV感染と好酸球との因果関係について解析する目的で，好酸球顆粒蛋白とRSV感染気道上皮細胞との相互関係について実験を行った結果，若干の知見を得ることができたのでその概要を報告する。

材料および方法

細胞培養

気道上皮細胞としてA549細胞 (ATCC CCL-185) を選択し，常法に従い培養した。すなわち，EDTA加0.1%トリプシン (Trypsin250, BD) 溶液を用いて剥離したA549細胞を，ダルベッコ変法イーグル培地 (D-MEM, 日水) を用いて培養した。D-MEM にはゲンタマイシンを20 μg/ml濃度に，牛胎児血清 (FBS) を10%濃度に添加して使用した。再浮遊した細胞は，組織培養用フラスコ (150cm^2) および96-well tissue culture plate (CORNING) にて37℃，5% CO_2条件下で細胞がconfluent になるまで培養した (72時間)。

形態学的変化

組織培養用フラスコ (150cm^2) から剥離したA549細胞液150mlを96-well tissue culture plateに100 μl/wellずつ分注し，37℃，5%CO_2条件下でインキュベーションした。各ウェル内の細胞数は，cell viability analyzer (Vi-CELL; BECKMAN COULTER) を用いて測定した。confluentとなった96-well tissue culture plateのウェルを滅菌リン酸緩衝液 (PBS) にて数回洗浄し，これにRSV (Long株) を感染させた。本実験に用いたRSVは，HEp-2 細胞で十分増殖させさらにA549細胞を用いたassayにより$TCID_{50}$ (Tissue Culture Infectious Dose 50%) を測定したウイルスを用いた (2.0x10^8 $TCID_{50}$/100 μl)。RSVは96-well tissue culture plate 各ウェルの細胞数から0.1，1.0あるいは10moi (multiplicity of infection) となるように適宜希釈して感染させた。RSV を感染させたA549細胞は，37℃，5% CO_2条件下で24 時間インキュベーションした。その後上清を廃棄し，4 種類のヒト好酸球由来高純度精製顆粒蛋白であるMBP，EPO，ECP (eosinophil cationic protein) およびEDN (eosinophil-derived neurotoxin) を添加した。これらの顆粒蛋白は，紀太博仁先生 (Department of Immunology, Mayo Clinic, U.S.A.) から分与していただいた。それぞれの好酸球由来顆粒蛋白濃度は0～50 μg/mlになるように2倍段階希釈して添加した (100 μl/well)。これらの顆粒蛋白添加後，37℃，5% CO_2条件下でさらにインキュベーションを実施し，経時的に顕微鏡下でA549細胞の形態学的変化を観察した。

細胞生存率

形態学的変化の方法と同様に，A549細胞にRSV (1moi) または好酸球顆粒蛋白 (25 μg/ml) を感染，添加し，24 時間後に96-well tissue culture plateの各ウェルから細胞を回収した。回収した細胞液はD-MEM にて1mlに調整後，Vi-CELLを用いて細胞生存率を測定した。

結　　果

0.1 および1moiのRSVを単独でA549細胞に感染させた場合，感染後48 時間までは非感染細胞 (Fig. 1A) と比較して有意な形態学的変化は生じなかった。10 moiのRSVを単独で感染させた場合は，48時間後に形態学的変化とcell free spaceが観察された (Fig. 1B)。また，各好酸球顆粒蛋白を単独で添加した場合，ECPとEDNについては，添加後72 時間まで今回実施した最高濃度 (50 μg/ml) においてさえも形態学的変化は観察されなかった。しかし，MBPおよびEPO を単独で添加した場合では，添加24時間後には比較的高濃度 (25 μg/ml以上) で，好酸球顆粒蛋白自身がA549細胞に形態学的変化を与えることが観察された。

一方，事前に0.1～10moiのRSVを24時間感染させたA549細胞に好酸球顆粒蛋白を添加した場合は，RSV感染量に依存して，低濃度のMBP とEPOでもA549 細胞へ傷害を与えることが観察された (Fig. 1C, Fig. 1D)。しかし，ECPとEDNにはその作用が確認されなかった。

好酸球顆粒蛋白添加24 時間後の細胞の生存率をFig. 2に示した。RSV感染単独の場合は，コントロールと比較して生存率に変化はみられなかった。また，好酸球顆粒蛋白を単独に添加した場合は，ECP，EDNの添加では変化はみられなかったが，MBPとEPOの添加で

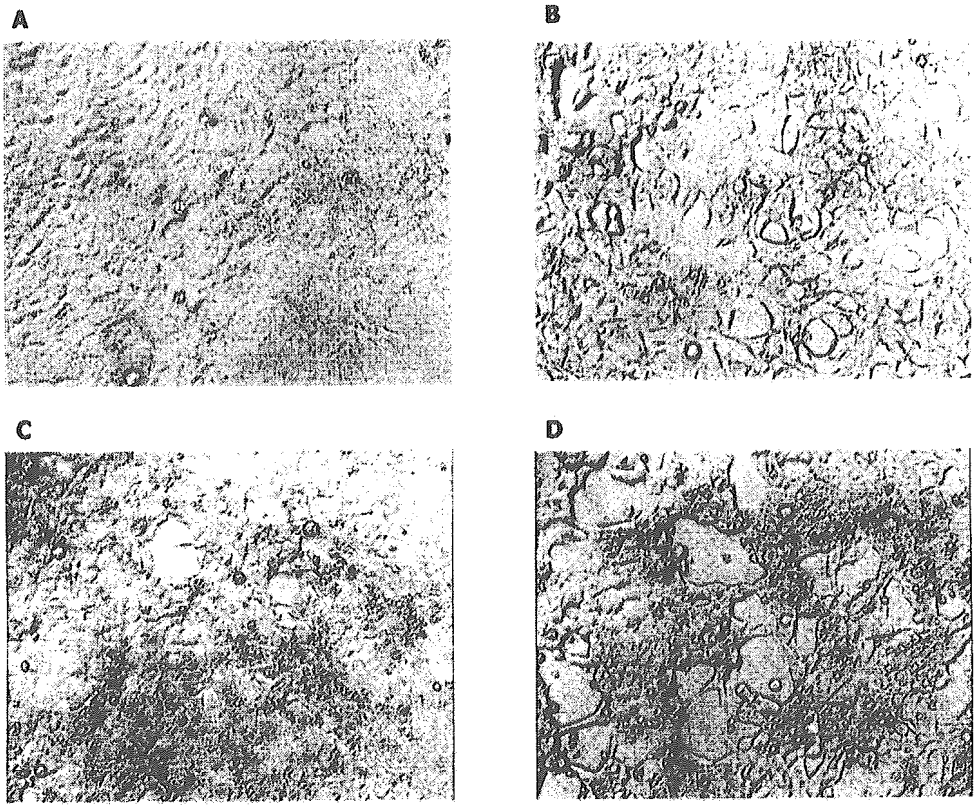

Fig. 1A. Non-infected and treated A549 cells (control).
Fig. 1B. A549 cells were infected with RSV (10 moi) for 48 hours.
Fig. 1C. A549 cells were infected with RSV (1 moi). Then the cells were treated with MBP (50μg/ml) after 24 hours.
Fig. 1D. A549 cells were infected with RSV (1 moi). Then the cells were treated with EPO (50μg/ml) after 24 hours.

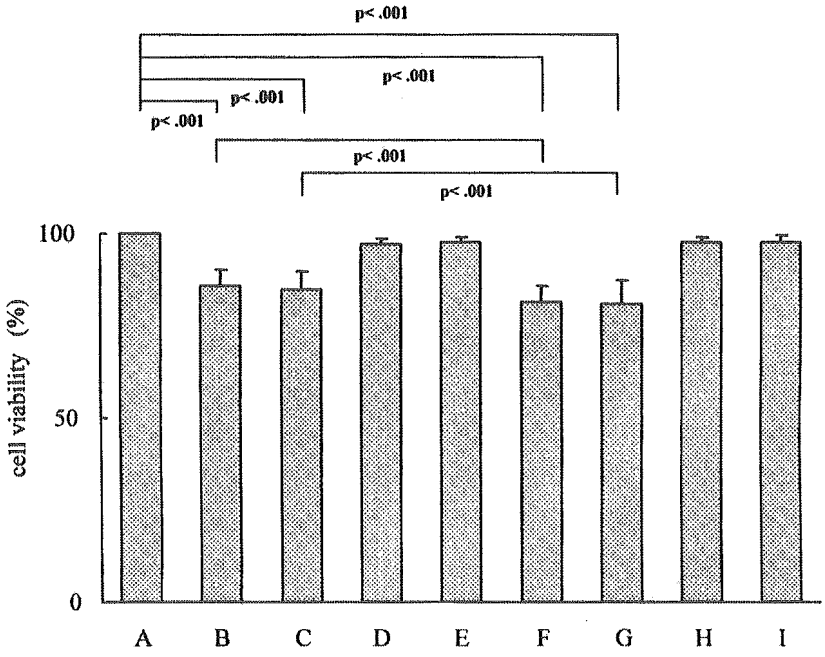

Fig. 2. The viability of A549 cells which were infected with RSV whose dose was 1 moi, or treated with four sorts of eosinophil granule proteins whose doses were 25μg/ml. Some samples of A549 cells were infected with RSV, and after 24 hours they were treated with four sorts of eosinophil granule proteins, such as MBP, EPO, ECP, and EDN, respectively. A, infected with RSV alone; B, treated with MBP alone; C, treated with EPO alone; D, treated with ECP alone; E, treated with EDN alone; F, infected with RSV, and after 24 hours treated with MBP; G, infected with RSV and after 24 hours treated with EPO; H, infected with RSV and after 24 hours treated with ECP; I, infected with RSV and after 24 hours treated with EDN. Statistical analysis was performed using the Bonferroni/Dunn's multiple comparison test.

は生存率が低下した。RSV感染後のMBPとEPO添加では，さらに生存率が低下した。

考　　察

好酸球顆粒蛋白は種々の細胞に傷害を与えることが報告されている[2,6]。我々の結果からも比較的高濃度のMBPおよびEPOはA549気道上皮細胞に傷害を引き起こすことが確認された。また，RSVを24時間感染させたA549細胞にMBPまたはEPOを添加した場合，好酸球顆粒蛋白単独で添加した場合よりも低濃度でA549細胞に形態学的変化を生じさせることが確認された。cell viability analyzerによる細胞生存率の解析においても，RSV感染後に好酸球顆粒蛋白を添加した方が，RSV感染単独の場合よりも細胞生存率の低下がみられた。これらの事象から，好酸球顆粒蛋白MBPおよびEPOはそれ自身でもA549細胞に傷害を与えうるが，RSVの感染により，より強い細胞傷害を引き起こす可能性が示唆された。RSV感染患者の多くは，炎症局所に多数の好酸球が浸潤している[9]。また，RSVの感染下においては，platelet-activating factor (PAF) などの脂質メディエーターの存在により好酸球が活性化され，そのため活性酸素の産生能が亢進する[13]ことなどからも，RSV感染後のMBPおよびEPO添加による細胞傷害性は，相加あるいは相乗的に増強することが推定された。これらの詳細な機序については今後十分検討する必要があると思われる。

一方，EDNとECPは，比較的高濃度でもRSV非感染および感染細胞両者に対して傷害を与えることは確認できなかった。このことから，A549細胞における好酸球顆粒蛋白による細胞傷害性は，主としてMBPとEPOが原因であることが示唆された。

近年，気道過敏症などを含むアレルギー反応においては，レアギン (IgE) ーマスト細胞が関与する即時型アレルギー反応よりも，むしろ主として好酸球が関与する遅発型アレルギー反応に対する関心が高まってきている[1,4]。好酸球の主な細胞性免疫機能である活性酸素生成，脱顆粒などのエフェクター機能は，気道過敏症などの炎症の場において重要な役割を果たし，ヒスタミンの遊離[15]，過剰な炎症反応の誘発，および病態の増悪に密接に関与する[7,13]。エフェクター機能の発現には，各種サイトカインやケモカインの産生[12]が必要であるが，我々の実験においても今後これらの測定が必要であると思われる。

以上のことから，好酸球は強塩基性である顆粒蛋白や活性酸素などのフリーラジカルを放出することで，微生物[8]や寄生虫[3]などを殺傷する。そしてその一方で，アレルギー反応においてはプロスタグランジン，ロイコトリエンおよび各種サイトカインを産生し[14]，肥満細胞，白血球，上皮細胞を過剰に活性化して炎症反応を増幅し，これらのことが，喘息の発症または憎悪に深く関与しているものと思われる。

今後これらの研究を進めていき，感染喘息における好酸球の機能および役割を解明していくことが重要であると考えられる。

謝　　辞

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Phase II Clinical Study of Cladribine in the Treatment of Hairy Cell Leukemia

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Abstract

We conducted a phase II clinical study to evaluate the therapeutic efficacy of cladribine (2-chlorodeoxyadenosine [2-CdA]) in the treatment of Japanese patients with hairy cell leukemia (HCL). Seven patients with classic HCL and 3 with a prolymphocytic HCL variant were administered 2-CdA (0.09 mg/kg per day) by continuous intravenous infusion for 7 days. Seven patients responded to this therapy, with 5 patients achieving a complete response (CR). After a median follow-up of 792 days (range, 599-1253 days), there were no cases of clinical relapse, and the median duration of the response in the responders was 670+ days (range, 470+ to 1121+ days). The median duration of the CR in the CR patients was 953+ days (range, 480+ to 1121+ days). At treatment initiation, most patients had hematologic impairment as a manifestation of HCL. During the early stage after administration, further hematologic impairment occurred, but subsequent peripheral blood counts gradually recovered as 2-CdA treatment showed antitumor activity. Infections occurred at a high incidence at this time, but all cases could be controlled with appropriate treatment. 2-CdA was surmised to represent a useful therapeutic approach for Japanese patients with HCL.
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Key words: Cladribine; 2-Chlorodeoxyadenosine; Hairy cell leukemia; HCL; Phase II clinical study

1. Introduction

Hairy cell leukemia (HCL) is a relatively rare form of leukemia, accounting for only approximately 2% of all leukemias in Europe and the United States [1]. Anemia, leukopenia, and thrombocytopenia are characteristic of HCL, and pancytopenia is present in two thirds of the patients. The incidence of HCL is far lower in Japan than in Europe and the United States. On the basis of the reports by Kitani et al [2,3], fewer than 200 patients are thought to have received HCL diagnoses during the 3 decades after the first Japanese patient with HCL was reported. Cladribine (2-chlorodeoxyadenosine [2-CdA]) is a chlorinated purine analog that is resistant to degradation by adenosine deaminase. 2-CdA accumulates to a high concentration as the 5′-triphosphate form (ie, 2-CdATP) in lymphocytes that have a high deoxycytidine kinase activity relative to 5′-nucleotidase activity. Accumulated 2-CdATP has been proposed to inhibit DNA synthesis in dividing cells by inhibiting ribonucleotide reductase and DNA polymerase α and is thought to inhibit the repair of DNA strand breaks and induce apoptosis in nondividing cells [4]. Recently, 2-CdA has been shown to also act as a transcriptional antagonist [5]. 2-CdA is thus distinguished from other chemotherapeutic agents by its unique characteristic of showing similar cytotoxic activities toward dividing and nondividing cells. Therefore, it is

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used for the treatment of indolent lymphoid malignancy, which is characterized by slow progression. In 1990, Piro et al at Scripps Clinic in the United States reported the first results for the use of 2-CdA in the treatment of HCL [6]. Their data revealed that only 7 days of continuous intravenous 2-CdA infusion were required to induce 11 complete responses (CRs) in 12 patients. These investigators subsequently reported a response rate of 97% (139 of 144 patients), including long-lasting CR in 122 patients (85%) [7]. Thereafter, 2-CdA was positioned in Europe and the United States as the drug of first choice for the treatment of HCL. The present phase II clinical study was designed with the objective of evaluating the efficacy of 2-CdA monotherapy in the treatment of Japanese patients with HCL.

2. Patients and Methods

2.1. Patients

The patients enrolled in this clinical study were selected on the basis of demonstration by central review of hairy cells in the bone marrow or peripheral blood and their conformity with the following inclusion criteria: (1) presence of evaluable lesions; (2) no interferon α (IFN-α) treatment within 2 months, no deoxycoformycin (DCF) treatment within 3 months, and no other antitumor therapies within the 4 weeks prior to the study; (3) a life expectancy of at least 3 months; (4) a performance status of 2 or better on the Eastern Cooperative Oncology Group scale; (5) an age ≥15 years and <85 years; (6) adequate hepatic and renal functions; and (7) written informed consent.

2.2. Drug Formulation

2-CdA was supplied by Janssen Pharmaceutical (Tokyo, Japan) as a 0.1% (1 mg/mL) solution of endotoxin-free 2-CdA in sterile 0.9% sodium chloride. The desired dosage of 2-CdA was added to preservative-free normal saline for a total volume of 500 to 1000 mL and was infused via central or peripheral venous access.

2.3. Study Design

This study was a multicenter phase II study to evaluate the therapeutic efficacy of 2-CdA in Japanese patients with HCL. The protocol of this clinical study was approved by the institutional review board of each institution. Because HCL is an extremely rare disease in Japan [2,3] and because we expected the accrued number of patients to be very small, we did not calculate the required number of patients for this study from expected and threshold response rates. We administered 2-CdA at a dosage of 0.09 mg/kg per day by continuous intravenous infusion for 7 days. This dosage was based on the results of a preceding phase I study in Japan [8]. This dosage is the same as the commonly used dosage in Europe and the United States. Efficacy was assessed at 4 months after the start of therapy.

2.4. Response and Toxicity Criteria

Tumor response was assessed according to the following criteria. CR was defined as the disappearance of hairy cells from the peripheral blood and bone marrow, disappearance of lymph node swelling, splenomegaly, and hepatomegaly, and normalization of the neutrophil count (≥1500/μL), the platelet count (≥10.0 × 10^4/μL), and the hemoglobin level (≥12 g/dL). Partial response (PR) was defined as a decrease of ≥50% in the hairy cells in the peripheral blood and bone marrow, a decrease of ≥50% in lymph node swelling, splenomegaly, and hepatomegaly, and normalization of the neutrophil and platelet counts. All other categories of tumor response were defined as no response (NR). Relapse was defined as a >50% increase in the hairy cell count in the bone marrow (ie, pathologic relapse) or a failure to maintain peripheral blood PR criteria (ie, clinical relapse). Assessment of the safety of the therapy was carried out by using the Japan Clinical Oncology Group's toxicity-grading criteria, which are an expanded version of the National Cancer Institute Common Toxicity Criteria [9].

2.5. Statistical Analysis

Analysis of the response rate was carried out by using point estimates and the 90% confidence interval (CI) of the response rate. The exact CI was used. The duration of the response was defined as the number of days from the first day of confirmation of the CR or PR until the day when relapse was diagnosed or until the final day of observation. The minimum and maximum values for the duration of the response were determined, and the Kaplan-Meier method was employed to estimate the 25%, 50%, and 75% points and their 90% CIs [10]. For analysis of the $CD4^+$ and $CD8^+$ cell count data, basic statistics were determined at baseline and at 15 days, 29 days, and 2, 3, and 4 months after the start of 2-CdA administration.

3. Results

3.1. Patient Characteristics

Ten patients were enrolled in this study from September 1996 through March 1999. All 10 patients satisfied the aforementioned eligibility criteria, underwent treatment, and became evaluable for the efficacy and safety of the therapy. Table 1 presents the clinical characteristics of the patients and their responses to 2-CdA treatment. The median age was 59.5 years (range, 28-76 years), and the central review of the disease type by hematopathologists revealed 7 cases of classic HCL and 3 cases of a prolymphocytic variant of HCL. Classification of the clinical stage according to the clinical staging system of Jansen et al [11] showed 3 cases each of stages I, II, and III. The remaining case was of a patient who had undergone splenectomy and received a classification of stage C. Tumor cells were morphologically identified in the peripheral blood of 9 of the 10 patients.

Table 1.
Patient Characteristics*

Case No.	Age,y/ Sex	Diagnosis	CD Phenotype			Clinical Stage	Splenomegaly	Prior Regimen (Response)	Hematologic Parameters (Baseline)				Cladribine Treatment Cycles, n	Response
			CD11c	CD19/20	CD25				Peripheral Blood Tumor Cells, /μL	ANC, /μL	PLT, $\times 10^4$/μL	Hb, g/dL		
H-01	59/F	HCL, prolymphocytic variant	+	+	−	III	4fb	CHOP (PR), IFN-α (NR), DCF (NR)	217,815	4468	12	7.8	2	NR
H-02	63/M	HCL, classic type†	+	+	−	I	2fb		3639	800	7.6	11.9	2	NR
H-03	61/F	HCL, classic type	+	+	+	II	16.0 cm‡	Prednisolone (NR)	532	294	3.5	7.0	1	CR
H-04	36/M	HCL, classic type	+	+	+	I	−		1811	1861	7.0	12.4	1	CR
H-05	49/M	HCL, classic type	+	+	+	III	5fb		4430	1175	2.3	8.3	1	CR
H-06	28/M	HCL, classic type	+	+	+	I	4fb	IFN-α (PR)	128	1448	5.4	17.1	1	CR
H-07	76/F	HCL, prolymphocytic variant	+	+	−	III	8fb		123,327	5276	12.5	8.7	1	PR
H-08	71/F	HCL, prolymphocytic variant	+	+	−	II	4fb		89,669§	3257	3.1	9.7	1	NR
H-09	52/M	HCL, classic type	+	+	+	II	−		14,550	2516	15.7	8.1	1	CR
H-10	60/M	HCL, classic type	+	+	+	C	−	Splenectomy (PR)	480	270	6.0	9.0	1	PR

*None of the patients had lymph node swelling or hepatomegaly. ANC, absolute neutrophil count; PLT, platelet count; Hb, hemoglobin concentration; HCL indicates hairy cell leukemia; CHOP, regimen of cyclophosphamide, doxorubicin, vincristine (Oncovin), and prednisolone; PR, partial response; NR, no response; IFN-α, interferon α; DCF, deoxycoformycin; CR, complete response.

†Diagnosis based on the morphologic aspects and strong tartrate-resistant acid phosphatase activity.

‡Spleen size data based on computed tomography results.

§Lymphocyte count.

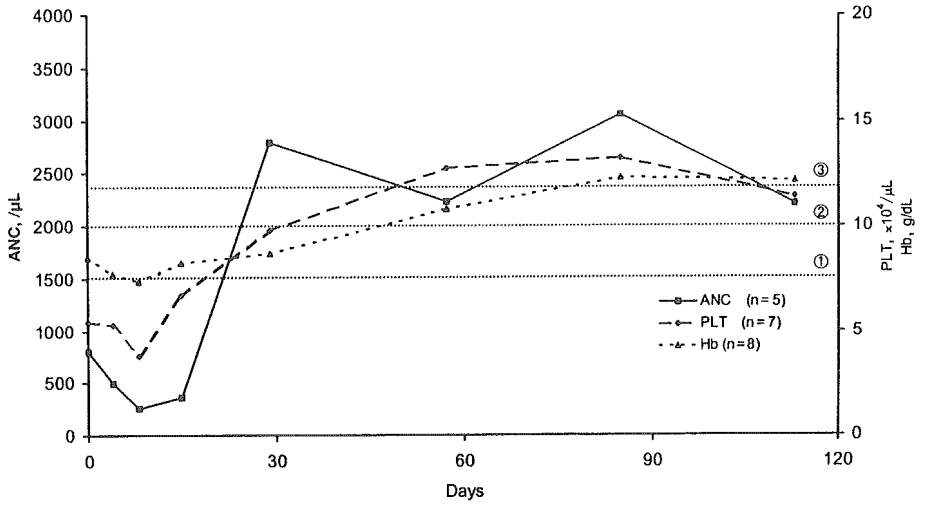

Figure 1. Time courses of changes in median values of hematologic parameters for patients with abnormal baseline values. Normal values (dotted lines): ① absolute neutrophil count (ANC), 1500/μL; ② platelet count (PLT), 10 × 10^4/μL; ③ hemoglobin (Hb), 12 g/dL.

3.2. Response

3.2.1. Response Rate

The response rate was 70% (90% CI, 39.3%-91.3%), and the CR rate was 50% (90% CI, 22.2%-77.8%). A response (CR + PR) was achieved in 6 (85.7%) of the 7 patients with diagnoses of classic HCL, and 5 (71.4%) of these patients achieved a CR. On the other hand, of the 3 patients with a diagnosis of a prolymphocytic variant of HCL, only 1 patient (33.3%) showed a PR. All of the responders achieved remission after 1 course of 7 days of continuous intravenous 2-CdA infusion, and this treatment showed efficacy in each of the clinical stages. One patient, who had previously been treated with IFN-α only, achieved a CR with 2-CdA chemotherapy. In contrast, another patient who had undergone previous therapy with 3 different regimens (ie, CHOP combination chemotherapy [cyclophosphamide, doxorubicin, vincristine, and prednisolone], DCF, and IFN-α) did not respond to 2-CdA.

3.2.2. Hematologic Response

Figure 1 shows the time courses of the median values of the hematologic parameters. Abnormal baseline values were observed for the neutrophil count, the platelet count, and the hemoglobin concentration in 5, 7, and 8 cases, respectively. Of the 5 patients with a CR, 3 were neutropenic, 4 were thrombocytopenic, and 3 were anemic at the time of treatment initiation. As shown in Figure 1, hematologic impairment as a manifestation of HCL worsened during the initial stage of 2-CdA treatment and then gradually recovered as 2-CdA showed antitumor activity. For the 5 CR patients, the median time required to achieve standard values for all 3 parameters was 83 days (range, 57-133 days); the median times for individual parameters were 126 days (range, 57-133 days) for the neutrophil count, 59.5 days (range, 15-63 days) for the platelet count, and 98 days (range, 83-133 days) for the hemoglobin concentration. Tumor cells in the peripheral blood disappeared in all 7 of the responders. In the 5 CR patients, tumor cell disappearance occurred during the early period after the start of 2-CdA chemotherapy, with the median time to disappearance being 15 days (range, 8-29 days).

3.2.3. Relapse, Duration of the Response, and Duration of CR

For the 7 responders, the median duration of follow-up was 792 days (range, 599-1253 days), and there were no cases of clinical relapse during that time. The median duration of the response in the responders was 670+ days (range, 470+ to 1121+ days), whereas the median duration of the CR in the CR patients was 953+ days (range, 480+ to 1121+ days).

3.3. Hematologic Toxicity

Adverse drug reactions (ADRs) with a severity grade of 1 or greater consisted of neutropenia in 8 patients (grade ≥3, 6 patients), thrombocytopenia in 2 patients (grade ≥3, 2 patients), and decreased hemoglobin concentration in 2 patients (grade ≥3, 2 patients). The times to the nadir and to the recovery or alleviation from the nadir were calculated for the 3 parameters in these 8 patients (Table 2). The median times to the nadir of the neutrophil count and to recovery were 15 days (range, 8-30 days) and 8 days (range, 8-50 days), respectively. The median times to the nadir of the platelet count and to recovery were 8 days (range, 8-8 days) and 11.5 days (range, 8-15 days), respectively. For the hemoglobin concentration, the median time to the nadir was 15 days (range, 15-15 days). The median time to recovery of the hemoglobin concentration was 29.5 days (range, 6-53 days). In all of the patients who showed bone marrow suppression, the nadir was reached within 1 month after the start of 2-CdA administration, and in all of these cases, this toxicity was reversible and manageable with the administration of a granulocyte colony-stimulating factor (G-CSF) preparation or a blood transfusion. In addition, significant decreases in the counts of

Table 2.
Hematologic Toxicity and Status of Recovery (First Cladribine Course)*

		Neutropenia	Thrombocytopenia	Hemoglobin Level Decreased
Time until Nadir†	Patients, n	8 (80.0%)	2 (20.0%)	2 (20.0%)
	Baseline	1655/μL (270-5276/μL)	5.7 × 10^4/μL (5.4-6.0 × 10^4/μL)	8.55 g/dL (8.1-9.0 g/dL)
	Time to Nadir, d	15 (8-30)	8 (8-8)	15 (15-15)
	Nadir	652/μL (39-1484/μL)	3.75 × 10^4/μL (3.7-3.8 × 10^4/μL)	6.4 g/dL (6.1-6.7 g/dL)
Status of Recovery‡	Patients, n	6 (75.0%)	2 (100.0%)	2 (100.0%)
	Time to Recovery, d	8 (8-50)	11.5 (8-15)	29.5 (6-53)
	Recovery	1936/μL (1020-4671/μL)	7.5 × 10^4/μL (6.7-8.3 × 10^4/μL)	10.05 g/dL (8.4-11.7 g/dL)

*Hematologic parameter data and times are expressed as the median (range).
†Numbers and characteristics of patients who showed hematologic toxicity severity of grade 1 or greater.
‡Numbers and characteristics of patients who showed recovery to baseline level or grade.

$CD4^+$ and $CD8^+$ cells were observed. In particular, the decrease in the $CD4^+$ cell count was prolonged (Figure 2).

3.4. Nonhematologic Toxicity

The most important nonhematologic ADR resulting from toxicity was infection. Seven patients developed infections within 1 month after the start of treatment. Infection was severe in 2 patients (1 case each of grade 4 sepsis and grade 3 pharyngitis). The other infectious complications, including 1 episode of herpesvirus infection, that occurred in the remaining 5 patients were all mild in severity. The patient who developed sepsis simultaneously developed grade 4 respiratory disorders (ie, dyspnea, hypoxia, and hypocapnia) and a grade 3 fever. The patient's performance status decreased, and administration of 2-CdA was discontinued after 5 days. The dyspnea was treated with oxygen inhalation and steroids and disappeared the day after its onset, and the fever and performance status improved. The hypoxia and hypocapnia also resolved after the sepsis had disappeared. In the second patient, the pharyngitis manifested on the eighth day after the start of 2-CdA chemotherapy, and treatment with antibiotics resolved the pharyngitis on the 29th day. Other nonhematologic toxicities, including nausea, vomiting, and elevation in liver enzyme levels, were of grade 2 severity or less. Almost all of the ADRs manifested within 1 month after the start of 2-CdA administration, and they were all manageable by means of appropriate treatment.

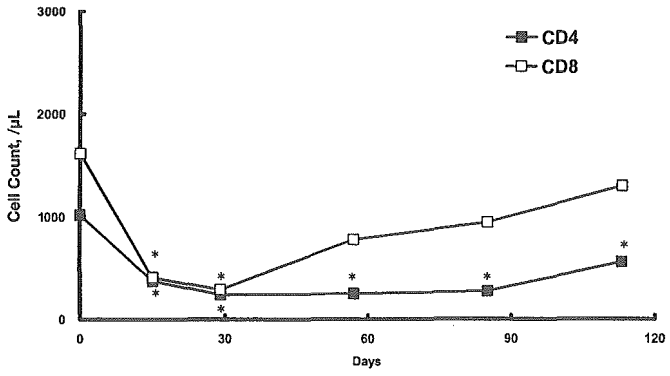

Figure 2. Time courses of changes in $CD4^+$ and $CD8^+$ cell counts (mean). *$P < .05$, Wilcoxon signed rank test for comparison of cell counts at the indicated time point and at baseline.

4. Discussion

The principal objective of this clinical study was to evaluate the efficacy of 2-CdA treatment for HCL in Japanese patients when administered at 0.09 mg/kg per day for 7 days by continuous intravenous infusion, a schedule that is in general use in other countries. The efficacy evaluation showed that 5 (50%) of 10 patients achieved a CR with only a single course of 2-CdA chemotherapy and demonstrated an overall response rate of 70%. The responders were subsequently followed up without administration of any maintenance therapy, and there were no cases of clinical relapse at a median follow-up period of 792 days (range, 599-1253 days). The median duration of the CR was approximately 32 months, and further follow-up is expected to show an even longer CR duration. Six (85.7%) of the 7 patients with diagnoses of classic HCL achieved a response, and 5 (71.4%) of these responders achieved a CR. These results confirm the extremely high antitumor efficacy of 2-CdA, as has also been shown in the clinical results reported in Europe and the United States [6,7,12-17]. On the other hand, only 1 (33.3%) of the 3 patients with a diagnosis of the prolymphocytic variant [18-21] achieved a response. Another variant form of HCL, the so-called Japanese variant, has been reported to occur in Japan. This variant differs considerably from classic HCL and the prolymphocytic variant, not only in relation to its clinical and hematologic pictures, but also in terms of its response to therapy [22-25]. Although 3 candidate patients with diagnoses of the Japanese variant were identified by central hematopathologic review at the time of screening, these 3 patients could not be enrolled in this study because 2 of the patients had few subjective symptoms and the other had multiple cancers.

The major 2-CdA toxicities observed in the present phase II clinical study of Japanese HCL patients were bone marrow suppression and infections, which are the same toxicities in the clinical results reported from Europe and the United States [7,12,13,16,17,26]. These complications were also the major 2-CdA toxicities reported in the results of phase II clinical trials for Japanese patients with adult T-cell leukemia-lymphoma and indolent non-Hodgkin's lymphoma [27,28]. At the initiation of 2-CdA chemotherapy, most

patients had hematologic impairment as a diagnostic characteristic of HCL. During the initial stage after the start of 2-CdA treatment, further hematologic impairment occurred, but the subsequent peripheral blood counts gradually recovered as the 2-CdA treatment showed antitumor activity. In addition, infections were diagnosed in 70% of the patients within 1 month of the start of treatment, but these infections proved manageable by means of suitable treatment, such as the administration of G-CSF and antibiotics. We advise that patients undergoing 2-CdA treatment be observed very carefully during the first month of the treatment. In addition, we observed a prolonged decrease in $CD4^+$ cell counts. In the present study, 1 patient who did not respond to 2-CdA developed acute myeloid leukemia (M3) and died during the treatment-free follow-up period, approximately 2 years after 2-CdA therapy. It remains unclear whether there is a tendency for the risk of developing secondary malignancies to increase as a result of the immunosuppression induced by 2-CdA therapy or whether any such increased risk is due to immunodeficiency caused by the primary disease.

In conclusion, our multicenter phase II study has demonstrated that a schedule of continuous intravenous 2-CdA infusion for 7 days at a daily dose of 0.09 mg/kg has definite efficacy and acceptable toxicity for the treatment of Japanese patients with HCL. We surmise that 2-CdA represents a useful therapeutic approach that induces a long-lasting complete remission with a shorter treatment duration, compared with conventional HCL chemotherapy, such as with IFN-α and DCF. However, further studies concerning the efficacy and the optimal treatment schedule of 2-CdA for the Japanese variant of HCL will be of importance.

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Review Article

Mild Cognitive Impairment after Adjuvant Chemotherapy in Breast Cancer Patients – Evaluation of Appropriate Research Design and Methodology to Measure Symptoms

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The development of new chemotherapeutic agents and regimens has contributed to reduced risk of cancer recurrence and prolonged patient survival. However, mild cognitive impairment (MCI), also known as "chemofog" or "chemobrain" following adjuvant chemotherapy for breast cancer has been reported since the late 1980s. Unfortunately, little is known about it's mechanism, type, severity, and episode length. This article reviewed related studies on the subject, and found that chemotherapy-induced MCI appears to occur in 10-40% of patients, and memory loss and lack of concentration are the most frequent symptoms. The symptoms are apparently transient, but take at least several years to disappear. Reviewed studies show a lack of clear understanding of what causes MCI directly. There is also a lack of consistency in symptom measurement. We point to the need to conduct well-designed studies which begin with a proper hypothesis. Future research needs to be randomized and longitudinal with a base measurement point before the chemotherapy cycle starts. Future studies must adopt an effective and sensitive method to measure MCI. The latest imaging technique, positron emission tomography (PET) may be a powerful tool. Also, all confounding factors, such as age, education, intelligence quotient (IQ), fatigue and depression, hormonal therapy and other treatments should be controlled within the study design. It is hoped that the results of such future studies will allow medical professionals to contemplate effective prevention, treatment and rehabilitation for MCI.

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Key words: Cognitive impairment, Chemotherapy, Breast cancer, QOL, PET

The development of new chemotherapeutic agents and regimens for breast cancer has contributed to reduced risk of recurrence and prolonged patient survival. However, mild cognitive impairment (MCI) following adjuvant chemotherapy for breast cancer, also known as "chemofog" or "chemobrain", has been referred to in scientific publications since the late 1980s, evoking interdisciplinary discussion on the subject[1, 2]. However, significant gaps exist in our understanding including the development mechanism, types, severity, and length of episode. The principal negative consequence is the deterioration of quality of life (QOL) of patients. In particular, for patients who hold professional and social positions, memory loss or concentration deficit may drastically affect their ability to fulfill work and social responsibilities[3]. MCI in older patients may have a long-term effect on survival or co-morbidity[4]. Information on QOL after chemotherapy can therefore be an important component in informed consent and decision-making[5].

The objective of this review article is to reorganize our actual knowledge on the issue of MCI

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Abbreviations:
MCI, Mild cognitive impairment; QOL, Quality of life

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and chemotherapy by focusing on its impact on patients' QOL and on an effective methodology to make clear MCI in breast cancer patients using the latest physiological function measurement methods.

Review Methodology

This study reviewed articles related to breast cancer, cognitive function and chemotherapy available in the MEDLINE database. After the search with these keywords, we selected articles for their relevance to the study aims and objectives. Finally, 10 studies which attempted to evaluate chemotherapy-induced MCI among breast cancer patients, organized in Table 1, were reviewed. The studies were a mixture of case-control and cohort studies.

MCI Observed Among Breast Cancer Patients

Frequency, Type and Grade of the Toxicity

The frequency of chemotherapy-induced MCI in breast cancer patients varies according to the studies reviewed; 20 to 30% in the study by Schagen[6], 34% in the study by Meyers[7], and 32% and 17% (high dose and standard dose, respectively) in the study by van Dam[8]. Most of these studies reported memory loss, lack of attention, and lack of ability to concentrate as symptoms (Table 1). Some of the observed symptoms in these studies are quantitatively difficult to measure, and sometimes go unnoticed by patients' family and friends.

Length of MCI Symptoms

The symptoms of chemotherapy-induced MCI are considered to be transient and reversible but persistent. A longitudinal study with two measurement points, the first point at two years after the end of the chemotherapy and the second point at four years[9], revealed that the symptoms were disappearing at the second measure of cognitive function. However, some studies still noted the problems in several patients almost 10 years after the end of the treatment[10, 11].

Regimen Differences: dose, Quantity

The examined studies reported that CMF (cyclophosphamide + methotrexate + 5FU), CEF (cyclophosphamide + epirubicin + 5-FU) and AF (adriamycin + 5-FU) were used as chemotherapy regimens. Actually, the difference in regimens did not clearly modify MCI in terms of occurrence rate, severity, length and type of symptoms, according to Schagen's study which compared regimens[9]. For quantity and cycle frequency of chemotherapy, van Dam found a dose-response relationship indicating that high-dose chemotherapy appeared to induce a much higher risk of MCI occurrence in comparison with control patients and patients receiving standard-dose chemotherapy[8].

MCI and QOL

Since chemotherapy-induced MCI is persistent but not fatal, its influence on QOL is of importance to patients who have long-term survival[12]. Harder's study found a correlation between QOL and cognitive function[13], and a similar result was found among elderly people in Logsdon's study[14]. Terada found a correlation between cognitive function and QOL among the elderly with dementia[15]. These studies thus support the fact that MCI has a considerable impact on patients' QOL.

In spite of different results in other cancer patient populations, none of the breast cancer studies reviewed identified a direct relationship between MCI and QOL, although several studies identify that chemotherapy itself significantly causes a deterioration in QOL scores. One matched case-control study could not identify a clear relationship between MCI and QOL measured using the FACT questionnaire[16], though patients receiving chemotherapy had a higher incidence of MCI and lower QOL scores. Brezden did not detect any difference in mood between the case and control group using an instrument to measure mood status, Profile of Mood States (POMS), although MCI had occurred significantly in a majority of cases[1]. Berglund compared QOL after adjuvant chemotherapy and postoperative radiotherapy[10]. His conclusion was that the differences between the two treatment groups were minimal, and the two groups did not report differences in memory and concentration.

We attribute the lack of evidence supporting the negative relationship of MCI to QOL to the fact that the disease-specific QOL questionnaires employed were not able to measure the difficulties patients face in resuming work or in daily communication. Dew reported in his study of patients undergoing heart transplantation that those with MCI are less likely to return to gainful employment, consequently reducing their QOL[17].

Table 1. Observed MCI in Breast Cancer Patients in Reviewed Studies

Author	Chemo-therapy regimen	Measure points	No. of subjects	Observed MCI		Cognitive Function Measures	QOL influence (measures)
				Symptom domain	Objective evaluation domain		
Tchen (2003)[16]	CEF/CMF /AC/Others	During	100 (chemo) 100 (ctrl)	–	Overall, Language	HSCS	Yes (FACT-F -ES)
Ahles (2002)[11]	CMF/CAF /Others	10 yrs	35 (chemo) 35 (local)	Working memory, new learning	Verval memory, psycho-motor performance	WAIS-III, WRAT-III, Saykin, CVLT, WMS-R	–
Svane (2002)[19]	CEF	2 yrs	52	–	memory	Common Toxicity criteria	–
Schagen* (2002)[9]	CMF/CTC /CEF	2 and 4 yrs	39 (CMF) 34 (CTC) 36 (CEF) 34 (ctrl)	Cognitive function	Attention, concentration, mental flexibility, speed of information processing, memory	RCF, WAIS, Trail Making (A/B), D2 Test, Stroop Test, Word Fluency Subtest of the Dutch Aphasia Society Test, Fepsy Test, Dutch Adult Reading Test Check list, Psychological Distress, Hopkins Symptom Checklist	Yes (EORTC QLQ-C30)
Brezden (2000)[1]	CMF/CEF	During and 2 yrs	31 (during), 36 (2yrs), 36 (ctrl)	–	Overall, memory, language, visual motor skill	HSCS, POMS	–
Schagen* (1999)[6]	CMF	2 yrs	39 : 34 (ctrl)	Cognitive function	Attention, concentration, mental flexibility, speed of information processing, memory	Idem*	Yes (EORTC QLQ-C30)
Van Dam* (1998)[8]	CTC/CEF	2 yrs	34 (high), 36 (std), 34 (ctrl)	Cognitive function	Concentration, memory, thinking	Idem*	Yes (EORTC QLQ-C30)
McLachlan (1998)[31]	N.A.	1 yr	57 (chemo), 93 (others)	N.S.	–	–	Yes (EORTC QLQ-C30)
Meyers (1992)[7]	GEM	2 to 10 yrs	47 (2 breasts)	–	Memory, frontal lobe function, visual-motor scanning, attention,	WAIS-R, WMS, Revised Benton Visual Retention Test, Trail Making (A/B), Grip strength, Finger tapping, Controlled Oral Word Association	–
Berglund (1991)[10]	CMF	2 to 10 yrs	201 (chemo), 172 (radio)	Smell aversion	–	HAD, Symptom list	N.S. (original measure)

HSCS = High Sensitivity Cognitive Screen, RCF = Rey Complex Figure, WAIS = Wechsler Adult Intelligence Scale, PASAT = Paced Auditory Serial Addition, COWAT = Controlled Order Word Association

*belongs to the same series of study