A Phase I-II Trial of Autologous Peripheral Blood Stem Cell Transplantation in the Treatment of Refractory Autoimmune Disease

Extended Report

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Running title: Autologous Stem Cell Transplantation for Autoimmune Disease

Key words: autoimmune disease, high-dose cyclophosphamide, interstitial pneumonia, transplantation, Wegener’s granulomatosis
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Abstract

Objectives. We performed a phase I-II trial to elucidate feasibility and efficacy of high-dose cyclophosphamide (CY) supported by autologous peripheral blood stem cell transplantation (PBSCT) in the treatment of severe and refractory autoimmune diseases (AD).

Methods. Peripheral blood stem cells (PBSCs) were mobilized during hematologic recovery after relatively high-dose CY (2 g/m² for 2 days) followed by administration of granulocyte colony stimulating factor (G-CSF). After collecting PBSC more than 2 x 10⁶ CD34+cells/kg by apheresis, CD34+ cells were immnologically selected and cryopreserved. Eight patients enrolled were systemic sclerosis (SSc) in 5, systemic lupus erythematosus (SLE) and SSc in 1, amyopathic dermatomyositis (ADM) in 1 and Wegener’s granulomatosis (WG) in 1. All of the patients were treated with high-dose CY (50 mg/kg for 4 days) and autologous PBSCT.

Results. Hematopoietic reconstitution was rapid and sustained. Regimen-related toxicity included various infections such as pneumonia, sepsis, cystitis, herpes zoster and acute heart failure. However, there was no treatment-related mortality. Encouraging results were obtained after autologous PBSCT. Sclerosis of the skin was markedly improved in all of the patients with SSc. When interstitial pneumonia (IP) was evaluated by PaO2, serum KL-6 levels and pulmonary HRCT, significant improvement was observed. In a patient with ADM, severe and progressive IP was also improved markedly. In a patient with WG, the size of the left orbital granuloma decreased substantially, which resulted in reduction of the exophthalmos.

Conclusions. These observations suggest that high-dose CY with autologous PBSCT is feasible and may be effective in the treatment of severe and refractory AD.

Key words: autoimmune disease, high-dose cyclophosphamide, interstitial pneumonia, transplantation, Wegener’s granulomatosis
Introduction

Although most patients with autoimmune disease (AD) have a relapsing, remitting or smoldering disease, some of them are severely damaged or fatal from the uncontrolled disease progression, and conventional therapies are not effective. The concept of high-dose immunosuppressive therapy and autologous hematopoietic stem cell transplantation (HSCT) for AD is based on the findings that HSCT is effective for animal models of AD (1-3), and that patients receiving autologous HSCT for treatment of malignant diseases can achieve long-term remission of coincidental AD (4-6).

Autologous HSCT as a treatment of AD was initiated in 1996, and more than 800 patients with AD have been treated (7). Clinically significant responses were observed in two thirds of the patients transplanted and treatment-related mortality (TRM) was reported to be relatively high (9%) in the early period until 2000 (8). The mechanism for inducing remission in AD is based not only on the eradication of autoreactive lymphocytes by an immunoablative pretransplant conditioning regimen, but also on the correction of dysregulated immune balance by newly developed lymphocytes derived from hematopoietic stem cells transplanted (9).

There were many reports addressing clinical results of autologous HSCT for AD. However, few studies provided detailed information concerning an effect of autologous HSCT on the interstitial pneumonia (IP), which is frequently associated with AD. In the study by McSweeney et al., 19 patients with systemic sclerosis (SSc) were treated with high-dose immunosuppression followed by autologous HSCT, resulting in no significant changes in carbon dioxide diffusion lung capacity (DLCO) or vital capacity (VC) at 12 months after autologous HSCT (10). We underwent a phase I-II trial to elucidate feasibility and efficacy of high-dose cyclophosphamide (CY) supported by autologous peripheral blood CD34-selected stem cell transplantation (PBSCT) in patients with severe and refractory ADs. We report encouraging results obtained in 8 patients, suggesting that high-dose CY with autologous PBSCT may be effective for treatment of AD complicated by IP.

Patients and Methods

Protocol

The protocol of this phase I-II clinical trial was approved by the ethics committee of Kyushu University Hospital. Written informed consent was obtained from all
Patients.

Patients and Eligibility

Patients aged between 16 and 65 years old were eligible at the time of pretransplant evaluation. Patient eligibility was prepared depending on diagnosis of AD. All of the patients were followed up for at least 12 months after transplantation for the evaluation of treatment outcomes.

Patients with SSc were eligible when they had severe diffuse SSc that had rapidly developed over the previous 4 years. They also had to have at least one of the following organ involvements: 1) pulmonary involvement included vital capacity or carbon dioxide diffusion lung capacity (DLCO) below 70% predicted or PaO$_2$ at room air below 70 mmHg and evidence of interstitial lung disease defined by pulmonary high-resolution computed tomography (HRCT), 2) cardiac involvement was reversible congestive heart failure or significant arrhythmia, and 3) renal involvement such as hypertension, persistent urinalysis abnormalities, microangiopathic hemolytic anemia and renal insufficiency.

Patients with limited scleroderma were considered eligible when progressive and life-threatening interstitial pneumonia was present.

Patients with amyopathic dermatomyositis (ADM) were eligible when they had the following criteria: 1) clinical diagnosis of ADM by the criteria reported (11), 2) progressive and life-threatening IP that was refractory to conventional immunosuppressive therapy.

Patients with Wegener’s granulomatosis (WG) were eligible when they had the following criteria: 1) clinical diagnosis of WG by the criteria reported (12), 2) vasculitis or granuloma causing severe organ damage that was refractory to conventional immunosuppressive therapy.

Exclusion criteria

Patients were excluded from the study when they had uncontrolled arrhythmia, heart failure with left ventricular ejection fraction (LVEF) below 50%, mean pulmonary artery pressure above 50 mmHg, DLCO below 20% predicted and creatinine clearance below 40 ml/min/m$^2$. 
Peripheral blood stem cell (PBSC) mobilization, CD34-cell selection, and autologous PBSCT

Peripheral blood stem cells (PBSCs) were mobilized during hematologic recovery after relatively high-dose CY (2 g/m²) for 2 days followed by administration of recombinant human granulocyte colony stimulating factor (G-CSF, filgrastim, Kirin Brewery, Tokyo, Japan) at a dose of 10 µg/kg as previously described (13). After collecting PBSCs to obtain 2x10^6 CD34+ cells/kg or more by apheresis, CD34+ cells were positively selected using an immunomagnetic beads with an anti-CD34 monoclonal antibody (CliniMACS, Miltenyi Biotec, Germany). Mobilization of PBSCs was repeated when 2x10^6 CD34+ cells/kg were not obtained. For pretransplant conditioning, high-dose CY (50 mg/kg) was given for 4 days from day –5 to –2. After transplantation of frozen-thawed CD34+ cells on day 0, G-CSF was administered from day 1. Acyclovir (250 mg/d, from day 1 to 18), ciprofloxacin (600 mg/d from day –7 to –1), fluconazole (400 mg/d from day –7 to 14, 200 mg/d from day 15 to 100), trimethoprim-sulfamethoxazole (1920 mg/d, from day –14 to –2 and 1920 mg/d, twice a week from day 30 to 100) were prophylactically given as previously described (13).

Treatment outcome

The modified Rodnan skin score (mRSS) was used to evaluate the improvement of skin sclerosis in patients with SSc (14). Arterial blood gas at room temperature, pulmonary function test, pulmonary HRCT and serological examinations were used to evaluate the effect of high-dose CY on IP. HRCT scans were graded and scored blinded according to the relative amount of ground-glass opacity and reticular infiltrates as follows: 1=pure ground-glass, 2=ground-glass more than reticular, 3=ground-glass equals reticular, 4=reticular more than ground glass, 5=pure reticular (15). The lower grade indicates more active inflammation in this system. Regimen-related toxicity (RRT) was determined and graded according to the National Cancer Institute (NCI)-Common Toxicity Criteria (CTC) version 2. Cytomegalovirus antigenemia was determined as previously described (16).

Statistical analysis

Wilcoxon’s signed rank test was used for statistical analysis of the data.
Results

Patients.

Eight patients were 3 males and 5 females, and their median age was 54 years (range 21-58) (Table 1). Patient 1-6 were diagnosed diffuse SSc. Patient 1 had had SLE for 22 years and SSc for 2 years. She suffered from progressive IP and severe digital ulcers due to SSc while SLE was inactive. Patients 2, 3, 5 and 6 (SSc) and 7 (ADM) also developed severe and progressive IP. Patient 4 had mild IP. Patients 3, 4, 5, and 6 showed severe skin sclerosis. Patient 3 had been in complete remission of non-Hodgkin’s lymphoma (NHL) for a year and he was considered to be eligible. Patient 8 (WG) presented with severe exophthalmos due to a granuloma which was 18 mm in diameter and located in upper lateral region of the left orbit involving superior rectus muscle. He needed monthly steroid pulse therapy to prevent the further growth of the granuloma. Eastern Cooperative Oncology Group performance status (17) was less than 3 in all patients. Anti-Scl 70 antibody was positive in 5 out of 6 SSc patients. CY and cyclosporin were used in 4 and 3 of the patients, respectively. All of the patients were treated with corticosteroid, and a median duration of follow-up was 21 months (range 13-33). Results were reported as of February 2005.

PBSC mobilization and CD34+cell selection

PBSCs were collected by apheresis after CY plus G-CSF-induced mobilization in all patients as previously described (13). A median number of total CD34+ cells collected was $7.61 \times 10^6$/kg (range 2.06-35.80) after apheresis (Table 2). CD34+cell selection was performed using CliniMACS. Purity and yield of CD34+ cells selected were 96.4 % (range 87.0-99.3) and 75.4 % (range 58.6-100), respectively. Mobilization was repeated in Patient 4 since a sufficient number of CD34+ cells ($\geq 2 \times 10^6$/kg) were not collected after the initial mobilization.

Autologous PBSCT

All of the patients received autologous transplantation of frozen-thawed CD34+ cells after pretransplant conditioning with high-dose CY. The numbers of CD34+ and CD3+cells infused were $4.92 \times 10^6$/kg (range 2.1-8.4) and $1.17 \times 10^4$/kg (range 0.27-13.0) respectively (Table 3). All of the patients achieved rapid hematopoietic engraftment. Median days to an absolute neutrophil count $>0.5 \times 10^9$/l and a platelet count $>50 \times 10^9$/l
were 10.5 (range 8-13) and 11.5 (range 9-20), respectively. Median days of interval between PBSC harvest and PBSCT was 50.5 (range 27-355).

Toxicity

Patients 1, 6 and 7 developed post-transplant infections and showed grade 3-4 toxicity according to NCI-CTC (Table 4). Patient 1 also developed pneumonia of unknown etiology and adenoviral cystitis, and Patient 6 showed positive blood cultures for Streptococcus mitis in addition to adenoviral cystitis. Adenoviral cystitis was successfully treated with Cidofovir. Patient 7 had positive blood cultures for Listeria monocytogenes. Four patients developed herpes-zoster with grade 2-3 toxicity around 12 months after transplantation. Five patients showed cytomegaloviral antigenemia. EBV titers were not checked in this study. Patient 1 had ventricular arrhythmia, and patient 4 showed ST depression in ECG during intravenous administration of CY. Patient 6 developed acute heart failure requiring temporary intubation after mobilization. Patient 2 was complicated by grade 3 bleeding from intestinal ulcer due to a non-steroidal anti-inflammatory drug during mobilization. Patient 5 showed hypoxia due to transient worsening of IP shortly after administration of G-CSF. All of the patients had grade 1-2 nausea and 5 patients showed grade 1-3 hepatic toxicity. Twelve months after autologous PBSCT, patient 3 experienced relapse of NHL that was successfully treated to reinduce complete remission by chemotherapy including Rituximab. All of the patients are alive with performance status 1 or 2.

Clinical outcome

SSc

For patients with SSc, posttransplant changes in mRSS are shown in Fig. 1. A decline in skin score is considered significant if it is greater than 25% of the baseline or greater than 10% of the maximum skin score. When this definition is used, 6/6 (100%) patients showed significant improvement. The mean skin scores at 1, 3, 6, and 12 months posttransplant were significantly less than those before mobilization (P<0.05). Five out of 6 patients showed improvement in skin score after mobilization before pretransplant conditioning although it was not statistically significant. Reincreases in skin score were not observed in all of three patients who were followed up for 18 months or more after autologous PBSCT (data not shown).
To investigate the effect of autologous PBSCT on IP, blood gas analysis, pulmonary function test and pulmonary HRCT were performed at 3 and 12 months after transplantation. As shown in Fig. 2a, PaO2 was significantly increased from the median value, 66.5 mmHg (range 51-88.7) before transplantation to 78.3 mmHg (69.7-102) and 83.2 mmHg (72.6-93.2) at 3 and 12 months after transplantation, respectively. Improvement of A-aDO2 was also observed in 4 patients at 12 months (Fig. 2b). The vital capacity (VC) was improved in 4 and 5 patients at 3 and 12 months, respectively (Fig. 2c). Improvement of DLCO was observed in only one patient (Fig. 2d). Serum levels of KL-6, a marker for IP (18), significantly decreased from the median value, 1823 U/ml (range 1080-2988) before transplantation to 890 U/ml (740-1962) and 989 U/ml (532-1273) at 3 and 12 months after transplantation, respectively (Fig. 2e). The ground-glass opacity markedly regressed in all of the patients although reticular infiltrates remained essentially unaffected after transplantation (Fig. 3), resulting in the significant improvement of pulmonary HRCT grading from the median value, 2.5 (range 2-3) before transplantation to 4 (range 3-4) at 12 months after transplantation (Fig. 2f).

ADM

Skin lesions had resolved by conventional immunosuppressive therapy before mobilization. PaO2 was increased from 65.6 mmHg before transplantation to 87.8 and 83.9 mmHg at 3 and 12 months after transplantation, respectively. VC was increased from 52.6 % to 59.3 and 74.1 % of the predicted value at 3 and 12 months, respectively. KL-6 decreased from 3280 IU/ml before transplantation to 1020 and 425 IU/ml at 3 and 12 months after transplantation, respectively. Both the ground-glass opacity and the reticular infiltrates were markedly improved in pulmonary HRCT at 12 months posttransplant. The clinical course of this case was described in detail elsewhere (19).

WG

The size of the left orbital granuloma markedly decreased, resulting in the improvement of the exophthalmos and regrowth of the granuloma has not been observed. Monthly steroid pulse therapy was not necessary to maintain this remission state. A serum level of PR3-ANCA decreased from 72 IU/ml before transplantation to 39 IU/ml at 3 months after transplantation. However, it increased again to 157 IU/ml 12
months after transplantation.

Discussion

In this study, we demonstrated that high-dose CY with autologous PBSCT was feasible and effective in the treatment of refractory AD. For patients with SSc, we have first demonstrated that high-dose CY and autologous PBSCT gave rise to favorable effects not only on skin sclerosis but also on IP. Our patient with WG is probably the first case that was treated with high-dose CY and autologous PBSCT (A first case with WG treated with high-dose CY and autologous PBSCT has been reported by Daikeler T et al. during the revision; Ann Rheum Dis, 2005; 64: 646-7).

We used a combination of high-dose CY and G-CSF to mobilize a sufficient number of PBSC without the disease flare, although G-CSF alone was able to mobilize PBSC (10). Flares of AD with the use of G-CSF have been reported in rheumatoid arthritis (20), multiple sclerosis (21) and SSc (22). In the European trial for SSc, the use of CY+G-CSF (84 % of the case) was preferred over G-CSF alone (10.7 %) (23). In our trial, one patient had to repeat the mobilization because a sufficient number of PBSC were not obtained by the initial mobilization. In another study, 1 of 12 PBSC mobilization failed with the same protocol and autologous bone marrow transplantation was subsequently performed instead (24).

We used immunological selection of CD34+ cells from PBSC harvests to minimize a risk of reinfusing autoreactive lymphocytes (25). The selection device (CliniMACS) permitted good yield and purity of CD34+ cells with few contaminated T cells. In a study of patients with malignancy and concomitant AD, a high rate of recurrent AD was observed when using unmanipulated autografts (26). In the European phase I–II trial for SSc, 47 out of 55 patients (85%) received CD34+ selection (23). On the other hand, a randomized trial of 31 patients with rheumatoid arthritis (RA) comparing T-cell depleted vs unmanipulated autologous PBSCT after high-dose CY (200 mg/kg) without additional T-cell purging agents failed to demonstrate significant differences between the two groups (27). The usefulness of T-cell depletion should also be investigated carefully in patients with other AD.

Six out of the 8 patients had infectious episodes. Viral infections were more common than bacterial infections. Other toxicity included cardiac toxicity of CY and temporary exacerbation of IP by G-CSF. Patient 6 developed acute heart failure...
requiring temporary intubation after mobilization, which might be due to the combination of viral myocarditis and cardiac toxicity of CY. She recovered from heart failure and received autologous PBSCT one year later. Patient 3 developed relapse of NHL. Relation of autologous PBSCT to relapse of NHL was not clear since autologous PBSCT was also used for treatment of NHL. There was no treatment-related or transplant-related mortality (TRM) in our study while an early European study and the study by McSweeney et al reported that the overall TRM was 9% and 15.8%, respectively (8, 10). One of the most important toxicities was cardiotoxicity, possibly related to direct CY toxicity and hyperhydration. The patient selection was reported to be important to reduce TRM (23) and a full cardiological assessment before transplantation was recommended by the European group (28). Careful patient selection, especially in the light of cardiac function evaluation, which is often underestimated in patients with severe rheumatic diseases, may have allowed us to avoid TRM.

Significant improvement in the skin score of >25% after autologous PBSCT occurred in all of the patients with SSc. In the European study and the study by McSweeney et al, it occurred in 69% and 100% of the patients transplanted, respectively (10, 29). The mechanism for the effect of autologous PBSCT on skin sclerosis may be due to intensive immunosuppression and immune reconstitution. In the European study and the study by McSweeney et al, 35% and 0% of the patients with an initial response relapsed during 20 and 14.7 months of median follow-up after transplantation, respectively (10, 23). A longer follow up is necessary to assess the response duration of skin sclerosis in our trial.

Improvement of IP has been demonstrated in patients with SSc and ADM whereas pulmonary function remained unaffected in other studies (10, 23, 29). In this study, PaO2, KL-6 and pulmonary HRCT grading were significantly improved, while DLCO values showed no significant change. KL-6 is a high-molecular-weight glycoprotein recently identified in humans as MUC1 mucin. It is a useful marker in the evaluation of disease activity not only of idiopathic pulmonary fibrosis but also of collagen vascular disease-associated interstitial pneumonia (30). VC was increased in 5 of 6 patients with SSc although it was not statistically significant. McSweeney et al treated 19 SSc patients with high-dose CY, total body irradiation (TBI) and ATG followed by autologous PBSCT and reported a significant decrease in the DLCO values at 3 months but not at 12 months and no significant change in the VC at 3 or 12 months after
Since IP was not evaluated with respect to PaO2, KL-6 or pulmonary HRCT grading in previous studies, the improvement of IP might have been undetectable. Selection biases of patients may be another reason; we may have selected patients with more active IP without honeycombing while more patients with inactive and stable IP may be selected in other studies. Difference of treatment-regimen, especially the usage of TBI may be responsible for the different results. It is reasonable that high-dose CY and autologous PBSCT could provide favorable effects on IP of SSc patients since intravenous pulse CY was reported to be effective for IP in patients with collagen vascular diseases including SSc (15, 31). In this study, improvement of DLCO was not observed, as seen in previous studies, in spite of the improvement of KL-6 and pulmonary HRCT grading. Since DLCO reflects not only interstitial lesions but also microvascular lesions of the lung (32), periphery-distributed microvascular impairment of the lung due to SSc may not have improved after autologous PBSCT compared with the improvement of interstitial lesions, resulting in the lack of improved DLCO.

In this study, a patient with WG that receiving autologous PBSCT was described. In European study, three cases of WG receiving autologous PBSCT were just listed, but the treatment outcome was not described (8, 33). In our case, G-CSF in combination with CY did not cause disease flare and high-dose CY with autologous PBSCT produced long-term remission for more than 16 months.

We did not incorporate anti-thymocyte globulin (ATG) in the conditioning regimen. Although ATG is believed to be useful to delete the residual T cells and is often used in the other settings (10, 23, 29), its usefulness has not been fully proved. Since we obtained significant clinical responses and considerable susceptibility to infections when treated with CY alone, ATG did not seem to be necessary. We did not incorporate TBI due to similar reason. Although our conditioning regimen was less intense than high-dose CY with ATG and/or TBI, initial clinical responses were comparable at least 12 month follow-up. It is important to look at response duration of our regimen in comparison with the more immunosuppressive regimens. A randomized controlled trial will be necessary to assess the usefulness of ATG and/or TBI.

Most of the patients showed the improvement of disease activity after high-dose CY and G-CSF for PBSC mobilization before pretransplant conditioning as shown in the previous study (34). Hematopoietic stem cells express high levels of aldehyde dehydrogenase, an enzyme responsible for cellular resistance to CY. Hence, high-dose
CY should have strong effects on fully differentiated and aggressive autoreactive lymphocytes and allow immune reconstitution by newly developed lymphocytes from CY-resistant hematopoietic stem cells (35).

In conclusion, the present phase I-II study demonstrated that high-dose CY with autologous PBSCT is feasible and effective in the treatment of refractory AD. We have first demonstrated the clinical effects of high-dose CY with autologous PBSCT on IP of SSc and on granuloma of WG. A prospective study with longer follow-up time and more patients will be necessary to assess the efficacy of this treatment modality in the treatment of AD.

Acknowledgements

We would like to acknowledge the cooperation of Dr. Kazuyoshi Saito, Dr. Isao Furugo, and Dr. Osamu Ushiyama for referring the patients for this study.

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Figure legends

Fig. 1. Evaluation of modified Rodnan’s skin score (mRSS). The serial skin score data are presented for 6 patients with SSc. The proportional change from baseline measurement was calculated for each patient at each available time point. The x axis is not drawn to scale. Data obtained before mobilization and just before conditioning are shown as “Pre” and “0” respectively. M, month.

Fig. 2. Evaluation of parameters associated with IP in 6 patients with SSc before mobilization, at 3 and 12 months after autologous PBSCT. (a) PaO₂ at room air, (b) AaDO₂, (c) vital capacity, (d) DLCO, (e) KL-6, (f) pulmonary HRCT grading. The x axis shows time. Data obtained before mobilization and just before conditioning are shown as “Pre” and “0” respectively. M, month.

Fig. 3. Pulmonary HRCT in patients with SSc. Upper panel, before mobilization; lower panel, 12 months after autologous PBSCT. (a) Patient 1, (b) Patient 2, (c) Patient 4.
References


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PS, performance status; mRSS, Modified Rodan skin score for systemic sclerosis; AD, autoimmune disease; F, female; M, male; SSc, systemic sclerosis; IP, interstitial pneumonia; ADM, amyopathic dermatomyositis; WG, Wegener’s granulomatosis; PR3, proteinase 3; St, corticosteroids; CY, cyclophosphamide; CsA, cyclosporine A
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Table 3. Number of reinfused cells and hematologic recovery

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<th>Patient</th>
<th>Number of reinfused CD34+ cells (x10^6/kg)</th>
<th>Number of reinfused CD3+ cells (x10^4/kg)</th>
<th>ANC &gt;0.5x10^9/l (day)</th>
<th>Platelet &gt;50x10^9/l (day)</th>
<th>Interval between PBSC harvest and PBSCT (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.4</td>
<td>0.33</td>
<td>9</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>4.9</td>
<td>0.27</td>
<td>9</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>2.2</td>
<td>2.95</td>
<td>10</td>
<td>12</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>2.1</td>
<td>1.71</td>
<td>11</td>
<td>16</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>7.2</td>
<td>13.00</td>
<td>13</td>
<td>9</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>4.0</td>
<td>2.35</td>
<td>11</td>
<td>11</td>
<td>355</td>
</tr>
<tr>
<td>7</td>
<td>4.9</td>
<td>0.50</td>
<td>8</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>5.0</td>
<td>0.52</td>
<td>13</td>
<td>11</td>
<td>50</td>
</tr>
</tbody>
</table>

ANC, absolute neutrophil count; PBSC, peripheral blood stem cell; PBSCT, peripheral blood stem cell transplantation
Table 4. Toxicity. (NCI)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Infection</th>
<th>CMV antigenemia</th>
<th>Cardiovascular</th>
<th>Hemorrhage</th>
<th>Pulmonary</th>
<th>Gastrointestinal (GI)</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pneumonia (3)</td>
<td>+ (2)</td>
<td>VPCs (3)</td>
<td>-</td>
<td>-</td>
<td>Nausea (2)</td>
<td>Elevated transaminase(1)</td>
</tr>
<tr>
<td></td>
<td>Cystitis, Adenovirus (3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>GI bleeding (3)</td>
<td>-</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td>3</td>
<td>H-Z (3)</td>
<td>+ (1)</td>
<td>-</td>
<td></td>
<td>-</td>
<td>(2)</td>
<td>(1)</td>
</tr>
<tr>
<td>4</td>
<td>H-Z (3)</td>
<td>+ (1)</td>
<td>Cardiac ischemia (2)</td>
<td>-</td>
<td>-</td>
<td>(2)</td>
<td>(2)</td>
</tr>
<tr>
<td>5</td>
<td>H-Z (3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Hypoxia (3)</td>
<td>(1)</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Sepsis, Strep. mitis (3),</td>
<td>+ (1)</td>
<td>CHF (4)</td>
<td>-</td>
<td>-</td>
<td>(2)</td>
<td>(3)</td>
</tr>
<tr>
<td></td>
<td>Cystitis, Adenovirus (3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Sepsis, Listeria monocytogenes (3), H-Z (2)</td>
<td>+ (2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(2)</td>
<td>(2)</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(1)</td>
<td>(2)</td>
</tr>
</tbody>
</table>

NCI, National cancer institute; CMV, Cytomegalovirus; H-Z, Herpes-Zoster; Strep, Streptococcus; VPC, ventricular premature capture; GI, gastrointestinal; CHF, congestive heart failure; (number), grade of toxicity
Change in mRSS (%) over time (months after PBSCT). The graph shows the percentage change in modified Rankin Scale (mRSS) for different patients over a 12-month period. The x-axis represents the time in months after PBSCT, with time points at Pre, 0, 1M, 3M, 6M, and 12M. The y-axis represents the change in mRSS in percentage. The graph includes data points for patients 1, 2, 3, 4, 5, and 6, indicated by different symbols. The P-value is less than 0.05, indicating statistically significant differences.
A Phase I-II Trial of Autologous Peripheral Blood Stem Cell Transplantation in the Treatment of Refractory Autoimmune Disease

Hiroshi Tsukamoto, Koji Nagafuji, Takahiko Horiuchi, Toshihiro Miyamoto, Kenichi Aoki, Ken Takase, Hideho Henzan, Daisuke Himeji, Takako Koyama, Katsuhisa Miyake, Yasushi Inoue, Hitoshi Nakashima, Takeshi Otsuka, Yoshiya Tanaka, Kohei Nagasawa and Mine Harada

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