Early Central Nervous System Complications after Reduced-Intensity Stem Cell Transplantation

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ABSTRACT
To investigate clinical characteristics of early central nervous system (CNS) complications after reduced-intensity stem cell transplantation (RIST), we reviewed the medical records of 232 patients who had undergone RIST for hematologic diseases at our institutions between September 1999 and June 2003. All patients had received purine analog–based preparative regimens. Stem cell sources comprised granulocyte colony-stimulating factor–mobilized blood from HLA-identical or 1 locus–mismatched related donors (n/H11549151), unrelated bone marrow (n/H1154944), or unrelated cord blood (n/H1154933). Graft-versus-host disease prophylaxis incorporated cyclosporine with or without methotrexate. Diagnosis of CNS complications was based on clinical, radiologic, and microbiological findings. CNS complications occurred in 18 patients (7.8%), with a median onset of 22 days, and were infectious (n/H115491), metabolic (n/H1154915), or cerebrovascular (n/H115492). Symptoms included seizures (n/H115497), visual disturbance (n/H115492), headache (n/H115498), nausea (n/H115498), vomiting (n/H115496), impaired consciousness (n/H1154916), and hemiparesis (n/H115493). Complications improved promptly in 10 patients, and 8 patients died without improvement within 30 days. Multivariate analysis with logistic regression identified umbilical cord blood transplantation as a significant risk factor for early CNS complications (odds ratio, 14.5; 95% confidence interval, 3.7-56.9; P < .0001). CNS complications are a significant problem after RIST, particularly with umbilical cord blood. Limbic encephalopathy is an unrecognized subtype of neurotoxicity after umbilical cord blood transplantation.

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KEY WORDS
Allogeneic hematopoietic stem cell transplantation ● Graft-versus-host disease ● Umbilical cord ● Cyclosporine neurotoxicity ● Limbic encephalopathy

INTRODUCTION
Research in the area of neurologic complications is limited with regard to allogeneic hematopoietic stem cell transplantation (allo-HSCT). Most studies have been either retrospective or reliant on autopsy records [1–6]. Prospective evaluation of this complication has been rare [7,8]. The incidence of neurologic complications has varied from 37% to 91%, and such complications have been the cause of death in 6% to 26% of patients [1,3,8]. These findings indicate that neurologic complications represent a significant problem in conventional myeloablative allo-HSCT.

Neurologic complications occur at 3 stages of allo-HSCT: (1) after the use of conditioning agents for marrow ablation, (2) during posttransplantation pan-
cytopenia, or (3) after immunosuppressive therapies and graft-versus-host disease (GVHD) [1–3,9]. These complications are usually categorized into 4 groups: (1) infectious, (2) cerebrovascular, (3) metabolic, or (4) immune-mediated disorders. Among these 4 types of neurotoxicity, cerebrovascular disorders and central nervous system (CNS) infection before engraftment have represented significant problems in conventional allo-HSCT [1,4,8]. Whether GVHD can affect the CNS remains controversial [10], and neurotoxicity has thus been regarded as an early complication after allo-HSCT.

A new transplantation strategy using a nonmyeloablative preparative regimen—reduced-intensity stem cell transplantation (RIST)—was developed to decrease regimen-related toxicity while preserving adequate antitumor effects [11,12]. Different pioneering conditioning regimens for RIST have been investigated, such as those including purine analogs [11–13] and total body irradiation (TBI) combined with potent immunosuppressants [14]. Although early reports on RIST emphasized safety advantages [11,15], recent studies have revealed considerable toxicities associated with this type of transplantation [16,17]. Little information is available on CNS complications after RIST. We investigated early CNS complications after RIST with regard to incidence, characteristics, and risk factors.

PATIENTS AND METHODS

Patients

Medical records of all patients who underwent RIST for treatment of hematologic diseases at the National Cancer Center Hospital or Toranomon Hospital between September 1999 and June 2003 were reviewed. Subjects comprised 232 patients (143 men and 89 women) with a median age of 54 years (range, 15-73 years). Primary diseases consisted of acute myeloid leukemia (n = 63), chronic myelogenous leukemia (n = 15), acute lymphoblastic leukemia (n = 8), malignant lymphoma (n = 67), myelodysplastic syndrome (n = 42), adult T-cell leukemia/lymphoma (n = 17), multiple myeloma (n = 10), aplastic anemia (n = 8), and others (n = 2). Hematologic malignancies were refractory to cytotoxic chemotherapy in 142 patients and were in remission or sensitive to treatment in 81 patients. Underlying diseases were not malignant in the remaining 9 patients.

Transplantation Procedures

All patients had received purine analog–based preparative regimens comprising fludarabine/cyclophosphamide (n = 12) [18], fludarabine/busulfan (n = 139) [19], fludarabine/melphalan (n = 55) [20], cladribine/busulfan (n = 25) [13], and others (n = 1). Rabbit antithymocyte globulin and TBI (4–8 Gy) were added to preparative regimens in 50 and 65 patients, respectively.

Stem cell sources were HLA-identical or 1 locus-mismatched granulocyte colony-stimulating factor-mobilized peripheral blood (n = 151), unrelated bone marrow (n = 44), or unrelated umbilical cord blood (n = 37). GVHD prophylaxis was cyclosporine alone (3 mg/kg) in RIST from an HLA-identical related donor and reduced-intensity umbilical cord blood transplantation (RI-UCBT). Patients who received transplants from a 1 locus–mismatched related donor or a matched unrelated donor received cyclosporine and short-term methotrexate. Grade II to IV acute GVHD was treated with methylprednisolone 2 mg/kg/d in addition to cyclosporine.

Diagnostic Criteria for Early CNS Complications

Early CNS complications were defined as CNS toxicity occurring within 100 days of transplantation. Diagnosis of CNS complications was made by clinical, radiologic, or microbiological findings (or a combination of these). CNS complications were categorized into 4 groups: (1) infectious, (2) cerebrovascular, (3) metabolic, and (4) immune-mediated disorders. CNS complications that occurred after relapse or progression of underlying diseases were excluded from analysis. Diagnosis of cyclosporine encephalopathy was based on the typical radiologic findings, ie, symmetrical white matter lesions mainly localized in the occipital lobe. In the case of limbic encephalopathy, the diagnosis was based on selective involvement of the medial temporal lobe on magnetic resonance imaging (MRI). Diagnosis of cerebrovascular diseases was confirmed by neuroradiologic or postmortem studies (or both). Abnormalities on imaging were defined as areas of low white-matter attenuation on computed tomographic (CT) scans and as areas of T1-weighted hypointensity and T2-weighted hyperintensity on MRI.

End Points and Statistical Analysis

The primary end point of this study was incidence of early CNS complications after RIST. A secondary objective was to investigate characteristics and risk factors for such complications. The median follow-up of surviving patients was 17.5 months (range, 8.5–52.7 months).

Univariate analysis with χ² and Mann-Whitney tests was performed to identify risk factors for CNS toxicity. Variables included age, sex, primary disease, disease status (refractory or sensitive to cytotoxic chemotherapy), and type of transplantation. We added multiple logistic regression analysis to assess the fractional contribution of the above-mentioned potentially predictive factors. Variables that had a P value of
In this study, CNS complications occurred in 7.8% of RIST recipients, and mortality with 30 days of its development reached 44%. These findings indicate that early CNS complications are a common and important problem in both RIST and conventional allo-HSCT [1,3,4,8]. However, significant differences existed in clinical characteristics of CNS complications between RIST and conventional myeloablative allo-HSCT.

The incidence of CNS complications was lower in RIST than in conventional allo-HSCT, in which 11% to 44% of patients develop such complications [2,6,7]. In conventional transplantation, the most common causes of CNS complications are cerebrovascular disease and infection after conventional transplantation [1,4,8], and these are mostly attributable to regimen-related toxicity [21,22] or profound myelosuppression before engraftment [1,3,4]. However, in RIST, regimen-related toxicities are minimal, and myelosuppression is short. Acute GVHD, as the most important complication in RIST [16], rarely affects the CNS [23]. RIST has, at the very least, improved the safety of allo-HSCT by decreasing the incidence of CNS complications.
Table 1. Backgrounds of Patients Who Developed CNS Complications after RIST

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Type of CNS Complication</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Primary Disease</th>
<th>History of CNS Involvement</th>
<th>No. of Chemotherapy Regimens before Transplantation</th>
<th>Preparative Regimen</th>
<th>GVHD Prophylaxis</th>
<th>Stem Cell Source</th>
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<tbody>
<tr>
<td>1</td>
<td>Cerebrovascular</td>
<td>57</td>
<td>M</td>
<td>ALL</td>
<td>Yes</td>
<td>1</td>
<td>Flu/BU/ATG</td>
<td>Cyclosporine</td>
<td>HLA-identical sibling</td>
</tr>
<tr>
<td>2</td>
<td>Cerebrovascular</td>
<td>32</td>
<td>F</td>
<td>Malignant lymphoma</td>
<td>No</td>
<td>1</td>
<td>Flu/Mel/TBI 4 Gy</td>
<td>Cyclosporine</td>
<td>Umbilical cord blood</td>
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<tr>
<td>3</td>
<td>Infectious</td>
<td>40</td>
<td>M</td>
<td>MDS</td>
<td>No</td>
<td>2</td>
<td>Flu/Mel/TBI 4 Gy</td>
<td>Cyclosporine</td>
<td>Umbilical cord blood</td>
</tr>
<tr>
<td>4</td>
<td>Metabolic</td>
<td>21</td>
<td>M</td>
<td>Aplastic anemia</td>
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<td>1</td>
<td>Flu/BU/ATG</td>
<td>Cyclosporine</td>
<td>HLA-identical sibling</td>
</tr>
<tr>
<td>5</td>
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<td>67</td>
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<td>Malignant lymphoma</td>
<td>No</td>
<td>1</td>
<td>Flu/Mel/TBI 4 Gy</td>
<td>Cyclosporine</td>
<td>Umbilical cord blood</td>
</tr>
<tr>
<td>6</td>
<td>Metabolic</td>
<td>51</td>
<td>M</td>
<td>MDS</td>
<td>No</td>
<td>2</td>
<td>Flu/BU/TBI 4 Gy/ATG</td>
<td>Cyclosporine/Methotrexate</td>
<td>Matched unrelated donor</td>
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<tr>
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<td>M</td>
<td>MDS</td>
<td>No</td>
<td>2</td>
<td>Flu/ATG</td>
<td>Cyclosporine</td>
<td>Mismatched related donor</td>
</tr>
<tr>
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<td>49</td>
<td>M</td>
<td>ALL</td>
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<td>1</td>
<td>Flu/BU</td>
<td>Cyclosporine</td>
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<tr>
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<td>F</td>
<td>AML</td>
<td>Yes</td>
<td>3</td>
<td>Flu/BU/ATG</td>
<td>Cyclosporine/Methotrexate</td>
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<td>F</td>
<td>AML</td>
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<td>Cyclosporine</td>
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<td>63</td>
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<td>54</td>
<td>M</td>
<td>AML</td>
<td>No</td>
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<td>Flu/Mel/TBI 4 Gy</td>
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<tr>
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<td>Metabolic</td>
<td>55</td>
<td>M</td>
<td>Malignant lymphoma</td>
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<td>1</td>
<td>Flu/Mel/TBI 4 Gy</td>
<td>Cyclosporine</td>
<td>Umbilical cord blood</td>
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<td>62</td>
<td>F</td>
<td>ATL</td>
<td>No</td>
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<td>Flu/Mel/TBI 4 Gy</td>
<td>Cyclosporine</td>
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</tr>
<tr>
<td>16</td>
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<td>M</td>
<td>ATL</td>
<td>No</td>
<td>1</td>
<td>Flu/Mel/TBI 4 Gy</td>
<td>Cyclosporine</td>
<td>Umbilical cord blood</td>
</tr>
<tr>
<td>17</td>
<td>Metabolic</td>
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<td>F</td>
<td>ATL</td>
<td>No</td>
<td>1</td>
<td>Flu/Mel/TBI 4 Gy</td>
<td>Cyclosporine</td>
<td>Umbilical cord blood</td>
</tr>
</tbody>
</table>

AML indicates acute myeloblastic leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; ATL, adult T-cell leukemia/lymphoma; Flu, fludarabine; BU, busulfan; ATG, antithymocyte globulin; TBI, total body irradiation; CNS, central nervous system.
| Patient No. | Type of CNS Complication | Cause | Onset (day) | Impaired Consciousness | Seizures | Visual Disturbance | Fever (>38.5°C) | Blood Pressure (Systolic, mm Hg) | Blood Pressure (Diastolic, mm Hg) | Cyclosporine (ng/mL)* | Laboratory Findings | Radiologic Examination | Electroencephalogram Outcomes | Outcomes |
|------------|-------------------------|-------|-------------|-----------------------|---------|-------------------|----------------|-------------------------------|-------------------------------|------------------------|------------------|-------------------|-----------------------|------------------|----------|
| 1          | Cerebrovascular         | 16    | No          | No                    | No      | No                | No            | 170                          | 87                            | 386                    | 0.6              | 9.0               | 139                   | 4.3              | 1.5               | NA                  | Subdural hematoma | NA Improved |
| 2          | Cerebrovascular         | 40    | Yes         | Yes                   | Yes     | Yes               | Yes           | 152                          | 98                            | NA                     | 1.6              | 7                 | 137                   | 3.5              | 1.3               | 217                 | Brain edema, subarachnoid hemorrhage | NA | Dead |
| 3          | Infection               | 68    | Yes         | Yes                   | No      | No                | No            | 108                          | 64                            | NA                     | 1.2              | 7.5               | 136                   | 3.4              | 0.6               | 140                 | Mass in the parietal lobe | NA | Dead |
| 4          | Metabolic encephalopathy| Cyclosporine | 8     | No          | No                    | No      | Yes               | Yes           | 142                          | 74                            | 316                    | 0.8              | 6.5               | 140                   | 4.0              | 1.5               | NA                  | Bilateral parietal and occipital lobe | NA | Improved |
| 5          | Metabolic encephalopathy| Limbic encephalopathy | 22    | Yes         | Yes                   | No      | No                | No            | 170                          | 108                           | 219                    | 0.3              | 8.2               | 124                   | 3.5              | 1.2               | 143                 | Bilateral temporal lobe | NA | Improved |
| 6          | Metabolic encephalopathy| Cyclosporine | 22    | Yes         | Yes                   | Not evaluable | Yes           | Yes           | 182                          | 100                           | 266                    | 1.2              | 7.5               | 141                   | 2.5              | 1.8               | NA                  | Low-density area in the bilateral occipital lobes | NA | Improved |
| 7          | Metabolic encephalopathy| Cyclosporine | 22    | Yes         | Yes                   | Not evaluable | No            | No            | 120                          | 80                            | 348                    | 1.5              | 6.5               | 139                   | 4.6              | 1.3               | 107                 | Normal | Bilateral occipital lobe | NA | Improved |
| 8          | Metabolic encephalopathy| Cyclosporine | 7     | Yes         | Yes                   | Not evaluable | Yes           | Yes           | 170                          | 70                            | 342                    | 0.8              | 4.1               | 138                   | 3.6              | 1.3               | 145                 | Normal | NA | Improved |
| 9          | Metabolic encephalopathy| Limbic encephalopathy | 46    | Yes         | No                    | Yes     | No                | No            | 130                          | 64                            | NA                     | 0.7              | 9.7               | 139                   | 4.1              | NA               | 110                 | Normal | NA | Dead |
| 10         | Metabolic encephalopathy| Limbic encephalopathy | 12    | Yes         | Yes                   | Not evaluable | Yes           | No            | 110                          | 56                            | NA                     | 1.1              | 6.5               | 134                   | 4.0              | NA               | NA                  | Normal | Bilateral frontal and parietal lobes (periventricular area) | NA | Dead |
| 11         | Metabolic encephalopathy| Limbic encephalopathy | 20    | Yes         | No                    | No      | No                | No            | 154                          | 100                           | 584                    | 0.8              | 8.2               | 130                   | 2.9              | 1.9               | 157                 | Normal | NA | Dead |
| 12         | Metabolic encephalopathy| Limbic encephalopathy | 13    | Yes         | No                    | Not evaluable | Yes           | Yes           | 190                          | 120                           | 511                    | 1.5              | 8.1               | 130                   | 4.2              | NA               | 162                 | Normal | Normal | Improved |
| 13         | Metabolic encephalopathy| Limbic encephalopathy | 24    | Yes         | No                    | No      | No                | No            | 158                          | 85                            | 60                     | 0.8              | 9.7               | 131                   | 4.3              | NA               | NA                  | Normal | Bilateral temporal lobe | Diffuse slow waves | Improved |
| 14         | Metabolic encephalopathy| Limbic encephalopathy | 22    | Yes         | No                    | Not evaluable | Yes           | No            | 168                          | 86                            | 416                    | 0.8              | 7.8               | 134                   | 3.9              | 1.3               | 107                 | Normal | Normal | Diffuse slow waves | NA | Dead |
| 15         | Metabolic encephalopathy| Limbic encephalopathy | 41    | Yes         | No                    | No      | Yes               | Yes           | 180                          | 120                           | 52                     | NA              | NA                | NA                   | NA               | NA               | NA                  | Normal | NA | Diffuse slow waves | Dead |
| 16         | Metabolic encephalopathy| Limbic encephalopathy | 26    | Yes         | Yes                   | Not evaluable | Yes           | Yes           | 174                          | 98                            | 37                     | 2.4              | 7.4               | 127                   | 3.4              | 1.4               | 130                 | Normal | Bilateral temporal lobe | Spike wave in frontal lobes | Dead |
| 17         | Metabolic encephalopathy| Limbic encephalopathy | 22    | Yes         | No                    | Not evaluable | No            | No            | 150                          | 100                           | 156                    | 0.4              | 9.7               | 113                   | 3.7              | NA               | NA                  | Normal | Normal | Diffuse slow waves | Improved |
| 18         | Metabolic encephalopathy| Limbic encephalopathy | 74    | Yes         | No                    | No      | No                | No            | 130                          | 80                            | NA                     | 2.2              | 12.1              | 119                   | 5.4              | NA               | NA                  | Normal | NA | Improved |

*Continuous infusion of cyclosporin was given at target levels of 250–350 ng/mL.

NA indicates not applicable; T-chol, total cholesterol.
In contrast to conventional allo-HSCT, the incidence of metabolic encephalopathy is increased with RIST. In this study, 15 of 18 CNS complications were metabolic. Of these patients, 4 were diagnosed with cyclosporine encephalopathy on the basis of typical clinical and imaging findings. The incidence of cyclosporine encephalopathy was 1.7% after RIST, which is comparable to that after conventional allo-HSCT in young patients [24]. The median onset was 15 days (range, days 7-22). Three patients displayed seizures and altered mental status that improved after discontinuation of cyclosporine. Blood levels for cyclosporine were normal in all of the 4 patients. Risk factors for cyclosporine encephalopathy have been reported [24,25], and hypertension (2/4), hypocholesterolemia (1/2), and hypomagnesemia (3/4) were observed in our study. These findings are comparable to previous reports on cyclosporine neurotoxicity [24,25]. The growing use of RIST has increased the chance of cyclosporine being administered to elderly patients. Our study does not support the hypothesis that cyclosporine neurotoxicity increases in elderly patients, but further investigation of the safety issues for cyclosporine is warranted. General management such as blood pressure control and electrolyte replacement may be important in preventing adverse effects of cyclosporine.

No findings in the remaining 11 patients with metabolic encephalopathy suggested cyclosporine encephalopathy. However, it should be noted that all 11 patients received a fludarabine-based preparative regimen and that fludarabine has a considerable neurotoxicity [26–32]. These findings suggest that fludarabine might have contributed to the development of CNS toxicity in this study. Except for 1 patient with leukoencephalopathy and hemophagocytic syndrome-related CNS complications, the other 10 patients had undergone UCBT. The incidence of CNS complications after RI-UCBT was 24%. Cord blood as a stem cell source was an independent risk factor in multivariate analysis (odds ratio, 14.5; 95% confidence interval, 3.7-56.9; \( P < .0001 \)). Few studies on CNS complications after myeloablative UCBT have been reported. This complication is possibly characteristic of RI-UCBT. All 10 patients developed altered mental status, including 3 with generalized seizures. Brain imaging in 3 patients showed abnormal signals around the hippocampus, whereas images were normal in the other 6 patients. Hippocampal encephalopathy in the 3 patients involved both white and gray matter and was thus distinct from leukoencephalopathy. Similar findings after RI-UCBT have recently been reported [33]. Although an association with tacrolimus administration has been suggested, none of our patients received tacrolimus, thus indicating other causes. Possibilities include infection, regimen-related toxicity, and immune reaction associated with the use of cord blood. Eight patients who developed metabolic encephalopathy after RI-UCBT had received fludarabine, melphalan, and TBI as a preparative regimen.

Figure 1. T2-weighted magnetic resonance image of the brain showing high-intensity signals in bilateral temporal lobes. The patient was diagnosed with limbic encephalopathy.
This has a higher intensity than most reduced-intensity regimens and might have caused CNS toxicities.

Conversely, CNS complications do not represent a significant concern in bone marrow or peripheral blood transplantation with similar reduced-intensity regimens. Because adult RI-UCBT recipients receive a relatively low dose of CD34+ cells, it would raise the concern that there might have been delayed engraftment, leading to an increase in subclinical and undetected CNS viral infections. However, this possibility seemed unlikely. In RI-UCBT with fludarabine, melphalan, and intermediate-dose TBI as a preparative regimen and cyclosporine as GVHD prophylaxis [34], the median day of neutrophil engraftment was 17.5 days. This is comparable to RIST with granulocyte colony-stimulating factor–mobilized blood [11,13]. Furthermore, neither cerebrospinal findings nor blood cultures identified CNS infection in our study, and no patient had GVHD at the onset of CNS complications. Because 4 of the 10 patients who underwent RI-UCBT died soon after the development of CNS complications, symptoms might represent an early manifestation of a systemic disorder predisposing for multiple organ dysfunction syndrome, increasing the risk of transplant–related mortality [35]. However, the association of CNS complications with engraftment is noteworthy in RI-UCBT. We did not use antithymocyte globulin or corticosteroids for preparative regimens or GVHD prophylaxis, respectively, although these practices have been commonly used in previous studies on UCBT [36]. Both agents display strong immunosuppressive properties. The fluid accumulation often observed during this period may have accentuated the tendency for brain edema to develop, as seen in patients with renal decompensation. In RI-UCBT with our regimens [34], the cumulative incidence of complete donor chimerism at day 60 was 93%, and the median time to complete donor chimerism was 22 days. Grade II to IV acute GVHD occurred in 27% of patients. Approximately 60% of RI-UCBT recipients had a noninfectious fever before engraftment (median onset, day 9). Manifestations included a high-grade fever, eruption, and diarrhea, and corticosteroids were effective for ameliorating these reactions. These findings suggest that they might be associated with a cytokine storm induced by massive proliferation of cells with a unique cytokine profile and that the CNS toxicity was attributable to these immune responses. We therefore treated the CNS toxicity with corticosteroids. Because CNS toxicity is associated with considerable morbidity and mortality, optimal preventive measures for CNS complications after RI-UCBT should be established. Intensification of GVHD prophylaxis, such as with methotrexate, might prove beneficial for this purpose.

This investigation was a retrospective study based on medical records. Pathologic examinations were not used in most patients, and diagnosis of CNS complications was established on the basis of clinical and radiologic findings. Mild neurotoxicity associated with allo-HSCT was likely neglected, and incidences might have been underestimated in this study. Compared with autopsy studies, approximately half of the patients with neurologic complications had been diagnosed during life [4]. Further prospective evaluation is warranted to clarify incidences and clinical characteristics for CNS complications after RIST and to establish optimal preventive and therapeutic measures.

In conclusion, we have demonstrated that CNS complications are a common and frequently fatal complication after RIST, particularly after the use of umbilical cord blood. Metabolic encephalopathy is the most common subtype of CNS complication after RIST, and it frequently manifests as limbic encephalopathy in RIST with umbilical cord blood.

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