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# Posterior Reversible Encephalopathy Syndrome after Hematopoietic Cell Transplantation in Children with Hemoglobinopathies

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A B S T R A C T

Posterior reversible encephalopathy syndrome (PRES) is a serious adverse event associated with calcineurin inhibitors used for graft-versus-host disease (GVHD) prophylaxis. We compared the incidence of PRES in children with thalassemia (n = 222, 1.4 to 17.8 years old) versus sickle cell disease (SCD; n = 59, 2 to 17 years old) who underwent hematopoietic cell transplantation from HLA-matched siblings or alternative donors and analyzed the risk factors for PRES. Overall, 31 children developed calcineurin inhibitor-related PRES (11%), including 30 patients with seizures and 1 patient without seizures. PRES incidence was significantly higher in SCD patients (22%; 95% confidence interval [CI], 10% to 32%) than in thalassemia patients (8%; 95% CI, 5% to 12%;*P* = .002). In multivariate analysis, factors associated with PRES were hypertension (hazard ratio [HR], 5.87; 95% CI, 2.57 to 13.43; *P* = .0001), SCD (HR, 2.49; 95% CI, 1.25 to 4.99; *P* = .009), and acute GVHD (HR 2.27; 95% CI, 1.06 to 4.85; *P* = .031). In the entire cohort overall survival (OS) was significantly higher in patients without versus with PRES (90% versus 77%; *P* = .02). In a subgroup analysis that including matched sibling transplants, OS and disease-free survival (DFS) were similar in thalassemia patients without PRES (92% and 88%, respectively) and with PRES (82% and 73%, respectively), whereas SCD patients with PRES had significantly lower OS (67%) and DFS (67%) than patients without PRES (94% and 94%, respectively; *P* = .008). Thus, SCD patients had a significantly higher incidence of PRES than thalassemia patients, and hypertension and GVHD were the 2 main risk factors for PRES in patients with hemoglobinopathies. Although PRES did not significantly influence survival in patients with thalassemia, patients with SCD had significantly lower survival after PRES.


## INTRODUCTION

Globally, thalassemia and sickle cell disease (SCD) are the most common types of hereditary hemolytic anemia. Hematopoietic cell transplantation (HCT) is the only well-established curative treatment for thalassemia and SCD and shows excellent long-term outcomes [1-6]. However, HCT is associated with transplant-related toxicities that can seriously compromise outcomes. The calcineurin inhibitors cyclosporine (CSA) and tacrolimus are the most frequently used agents for graft-versus-host disease (GVHD) prophylaxis, but both are associated with adverse effects, with neurotoxicity representing a significant complication of these immunosuppressive drugs.

Posterior reversible encephalopathy syndrome (PRES) is an increasingly recognized serious complication of CSA and tacrolimus use in HCT recipients. PRES is a clinical and neuroradiologic entity that is characterized by neurologic symptoms, including headache, visual disturbances, mental status changes, seizures, and coma. The overall incidence of

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PRES after HCT in children is reported to be 4.6% to 34%, and some reports suggest that PRES occurs more frequently in children with hemoglobinopathies undergoing HCT [7-12] than in those with other conditions [10,13]. Few studies have reported the risk factors for PRES in children after HCT, mainly because of the small number of patients. Furthermore, most studies included heterogeneous diseases and conditioning regimens that make it difficult to predict whether children with certain diseases are more predisposed to PRES than children with other diseases. Therefore, the present study investigated whether the incidence of PRES differed in patients with thalassemia versus SCD in a homogeneous patient population. We also evaluated the risk factors and described the clinical, radiologic, and electroencephalographic features of PRES in this population.

## METHODS

### *Patients and Donors*

Between July 2004 and April 2016, a total of 281 consecutive pediatric patients with thalassemia (n = 222) or SCD (n = 59) from 38 different countries underwent allogeneic HCT at the Mediterranean Institute of Hematology in Rome, Italy and were enrolled in the present study to assess neurotoxicity (Table 1). Of these, 202 patients received HLA-matched sibling transplants, 11 received HLA-matched related nonsibling transplants, 6 received 1-antigen mismatched related transplants, 10 received HLA-matched unrelated transplants, and 52 received haploidentical transplants. Thirteen patients received a second transplant.

The study was approved by the Mediterranean Institute of Hematology Institutional Review Board. The parents of all patients provided written informed consent in accordance with the Declaration of Helsinki.

### *Treatment Protocols*

All patients received busulfan/cyclophosphamide (BuCy)-based conditioning regimens (Table 1). A total of 70% of patients received fludarabine before the conditioning regimen for pretransplant cytoreduction/immunosuppression.

**Table 1**
Patient and Transplant Characteristics

| Variables | Thalassemia | SCD | *P* |
|---|---|---|---|
| Number of patients | 222 | 59 | |
| Median age, yr (range) | 8 (1.4-17.8) | 10 (2-17) | .01 |
| Male sex, n | 128 | 37 | .55 |
| Risk class | | | |
| Class 1, n | 47 | NA | |
| Class 2, n | 72 | NA | |
| Class 3, n | 103 | NA | |
| Indications for transplantation, n (%) | | | |
| Stroke | - | 6 (10) | |
| Silent cerebral infarcts | - | 14 (24) | |
| Recurrent vaso-occlusive crisis | - | 31 (52) | |
| Recurrent acute chest syndrome | - | 15 (25) | |
| Chronic blood transfusion | 222 | 13 (22) | |
| Recurrent splenic sequestration | - | 1 (1.7) | |
| Recurrent hand-foot syndrome | - | 1 (1.7) | |
| Recurrent priapism | | 1 (1.7) | |
| Median packed RBC units received pretransplant, n (range) | 70 (5-307) | 60 (9-120) | .012 |
| Median serum ferritin, ng/mL (range) | 1950 (279-11,815) | 549 (30-5591) | <.0001 |
| Median liver fibrosis score | 2 (1-5) | 1 (0-2)* | |
| Donor | | | .02 |
| Matched sibling, n | 151 | 50 | |
| Matched related nonsibling, n | 11 | 2 | |
| One-antigen mismatched related, n | 6 | - | |
| Matched unrelated, n | 10 | - | |
| Haploidentical, n | 45 | 7 | |
| Stem cell source | | | .07 |
| Bone marrow, n | 172 | 51 | |
| PBSC, n | 50 | 8 | |
| Graft type | | | .18 |
| T cell replete, n | 177 | 52 | |
| T cell depleted, n | 45 | 7 | |
| Donor–recipient sex match | | | .18 |
| Matched, n | 101 | 21 | |
| Mismatched, n | 121 | 38 | |
| Donor–recipient CMV status | | | .76 |
| Both positive, n | 173 | 47 | |
| Any positive, n | 16 | 5 | |
| Both negative, n | 33 | 7 | |
| Conditioning regimens | | | |
| BuCy200,† n | 31 | - | |
| BuTT10Cy200, n | 37 | - | |
| BuCy200ATG10-12.5, n | - | 17 | |
| BuCy200 preceded by Flu 150, n | - | 33 | |
| BuCy160 preceded by HuAzFlu cytoreduction/immunosuppression, n | 28 | - | |
| BuTT10Cy160 preceded by HuAzFlu cytoreduction/immunosuppression, n | 43 | - | |
| BuTT10Cy200ATG preceded by HuAzFlu cytoreduction/immunosuppression, n | 83 | 9 | |
| GVHD Prophylaxis: | | | .18 |
| CSA +Methylprednisolone + short MTX, n | 177 | 52 | |
| CSA +Methylprednisolone, n | 45 | 7 | |

NA indicates not applicable; PBSC, peripheral blood stem cell; CMV, cytomegalovirus; TT, thiotepa; ATG, antithymocyte globulin; Flu, fludarabine; Hu, hydroxyurea; Az, azathioprine; MTX, methotrexate.

* Liver biopsy was performed in patients on chronic blood transfusion.

† From July 2004 to June 2006 all patients received 14 mg/kg total dose of oral busulfan and weight-based i.v. busulfan thereafter.