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ORIGINAL ARTICLE

Hematopoietic cell transplantation for Chediak–Higashi syndrome

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We reviewed outcomes after allogeneic hematopoietic cell transplantation (HCT) in 35 children with Chediak–Higashi syndrome (CHS). Twenty-two patients had a history of the life-threatening accelerated phase of CHS before HCT and 11 were in accelerated phase at transplantation. Thirteen patients received their allograft from an human leukocyte antigen (HLA)-matched sibling, 10 from an alternative related donor and 12 from an unrelated donor. Eleven recipients of HLA-matched sibling donor, three recipients of alternative related donor and eight recipients of unrelated donor HCT are alive. With a median follow-up of 6.5 years, the 5-year probability of overall survival is 62%. Mortality was highest in those with accelerated phase disease at transplantation and after alternative related donor HCT. Only four of 11 patients with active disease at transplantation are alive. Seven recipients of alternative related donor HCT had active disease at transplantation and this may have influenced the poor outcome in this group. Although numbers are limited, HCT appears to be effective therapy for correcting and preventing hematologic and immunologic complications of CHS, and an unrelated donor may be a suitable alternative for patients without an HLA-matched sibling. Early referral and transplantation in remission after accelerated phase disease may improve disease-free survival.
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Introduction

Chediak–Higashi syndrome (CHS) is a rare autosomal-recessive disorder, characterized by oculocutaneous albinism, recurrent infections, microscopic finding of large granules in hematopoietic and other cells, bleeding diathesis and neurologic abnormalities.[1–3] Pathologic mutations in the lysosomal trafficking regulator gene localized to human chromosome 1q42-q43 are responsible for development of CHS.[4,5] Neutropenia and defects in natural killer cell activity, T-cell cytotoxicity, chemotaxis and bactericidal killing by granulocytes and monocytes result in increased susceptibility to infection.[6,7] In survivors of infectious complications, an accelerated phase, manifested by life-threatening hemophagocytosis, typically associated with Epstein Barr virus infection, occurs within the first or second decade. The accelerated phase of CHS is characterized by lymphocyte and macrophage activation with diffuse lymphohistiocytic infiltration of liver, spleen, lymph nodes, central nervous system and bone marrow. This is the most frequent cause of mortality in patients with CHS.[4,8] Transient remissions are reported after treatment with etoposide, corticosteroids and supportive care; relapses are frequent and are increasingly resistant to treatment.[9–11]

Published reports suggest that allogeneic hematopoietic cell transplantation (HCT) may be effective therapy for the accelerated phase of CHS; however, these studies are limited by small numbers of patients. Additionally, most reports describe outcomes only after human leukocyte antigen (HLA)-matched sibling transplants.[11–15] The purpose of this study was to determine whether similar outcomes could be expected after HLA-matched sibling, alternative related and unrelated donor transplants. In this retrospective descriptive analysis, we report outcomes after HCT for CHS in 35 patients transplanted between 1 January 1980 and 31 December 1999 and reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).

Patients and methods

Data collection

The CIBMTR is a working group of over 500 transplant centers worldwide that voluntarily contribute data on their allogeneic transplants to a Statistical Center at the Medical College of Wisconsin. Participating centers register and provide basic information on all consecutive transplantations. Detailed demographic, disease and transplant characteristics and outcome data are collected on a sample of registered patients including virtually all adult unrelated donor transplants in the US. Patients are followed longitudinally. Computerized error checks, physician review of submitted data, and on-site audits of participating centers ensure data quality.

Inclusion criteria

Patients with CHS transplanted in 1989–1999 and reported to the CIBMTR ($n=40$) were eligible for this study. Comprehensive pre- and post-transplant clinical information were available for 35 (88%) patients. The diagnosis of CHS was based on the constellation of clinical findings of oculocutaneous albinism, giant leukocyte granules, neutropenia, recurrent infections and neurological dysfunction with or without abnormal natural killer cell function. The cases in this review were ascertained before publication of the genetic defect responsible for CHS.

End points

Hematopoietic recovery was defined as achieving an absolute neutrophil count (ANC) of $\geqslant 0.5\times10^9$/l for three consecutive days and platelets $\geqslant 20\times10^9$/l. Diagnosis of acute and chronic graft-versus-host disease (GVHD) was based on local institutional criteria with overall grade assigned retrospectively by the CIBMTR based on stage of involvement reported for each individual organ.[16,17] Death from any cause was considered an event. Surviving patients were censored at last follow-up.

Statistical analysis

The probability of overall survival was calculated using the Kaplan–Meier estimator and the confidence interval, calculated with the use of a log transformation.[18] This was performed using the statistical package SAS version 9.1 (Carey, NC, USA).

Results

Patient and transplant characteristics

Patient and transplant characteristics are shown in Table 1. Median age at transplantation was 5 (range, 1–19) years. Before HCT, patients received variable treatments with corticosteroids, acyclovir, γ-globulin, etoposide, anti-thymocyte globulin and intrathecal methotrexate for management of clinical features of the disease. Twenty-two patients had a history life-threatening accelerated phase of CHS before transplantation and of these, 11 were in accelerated phase at transplantation. Ten patients were transplanted before development of symptoms or signs of accelerated phase and these data were not available for three patients. Thirteen patients received allografts from an HLA-identical sibling. Among recipients of alternative related donor transplants, three received allografts from an HLA-identical parent, three from a one-antigen mismatched parent or sibling, and the remaining four, from haplo-identical parents. Five received allografts from an HLA-identical unrelated donor and the remaining seven, from one-antigen mismatched donors (HLA A and B at the antigen level by intermediate resolution and allele-level DRB1). All received bone marrow grafts except 1 who received peripheral blood. Six bone marrow grafts were T-cell-depleted and included grafts from haplo-identical parent ($n=4$), one-antigen mismatched sibling ($n=1$) and matched unrelated donor ($n=1$). The most common preparative regimen utilized the combination of oral busulfan and intravenous cyclophosphamide. The median follow-up of the study population is 80 months (range 14–174).

Table 1 Patient and transplant characteristics

Variable	*Number of evaluation*	*Number (%)*
Number of patients	35	
Male sex	35	15 (43)
Age at transplant, years	35	
< 5		19 (54)
5–9		10 (29)
10–14		4 (11)
15–19		2 (6)
Karnofsky/Lansky score ⩾90	35	20 (57)
Time from diagnosis to BMT, median (range), months	27	5 (1–71)
Donor	35	
HLA-identical sibling		13 (37)
Other relative[a]		10 (29)
Unrelated donor[b]		12 (34)
Graft type	35	
Marrow		34 (97)
Peripheral blood		1 (3)
Preparative regimen	35	
Cy/TBI ± other[c]		11 (31)
Bu/Cy ± other[d]		23 (66)
Cy		1 (3)
Year of transplant	35	
1980–1989		8 (23)
1990–1994		13 (37)
1995–1999		14 (40)
GVHD prophylaxis	35	
Cyclosporine ± other[e]		11 (31)
Methotrexate ± other[e]		2 (6)
Cyclosporine/methotrexate ± other[e]		16 (46)
T-cell depletion ± other[f]		6 (17)

Abbreviations: Bu = busulfan; BMT = bone marrow transplantation; Eval = evaluable; Cy = cyclosporine; GVHD = graft-versus-host disease; TBI = total body irradiation.
[a]Other relative: one-antigen mismatch sibling ($n=1$) and nine parents. Three parents were HLA-identical, two were mismatched at one-antigen and the remaining four, greater than two-antigen mismatch.
[b]Unrelated: five were HLA-identical and the remaining seven, one-antigen mismatch.
[c]Other: cytosine arabinoside, etoposide, anti-thymocyte globulin, corticosteroids.
[d]Other: etoposide, anti-thymocyte globulin, corticosteroids.
[e]Other: anti-thymocyte globulin, corticosteroids.
[f]Other: cyclosporine.

Hematopoietic recovery

The median time to neutrophil and platelet recovery was 18 (range, 7–35) days and 32 (15–152) days, respectively. Two patients failed to achieve hematopoietic recovery; both received bone marrow grafts from alternative related donors. One patient died before second transplantation and the other underwent a second transplant, achieved hematopoietic recovery but died from persistent disease (day 47 after second transplant). Both patients were in accelerated phase at transplantation.

Graft-versus-host disease

Thirty-three patients were evaluable for acute GVHD. Recipients of unrelated donor HSCT were more likely to develop grade 2–4 acute GVHD (nine of 12); six patients developed grade 2 and 3 patients developed grade 3–4 acute GVHD. Four of eight recipients of alternative related donor HCT developed grade 2–4 acute GVHD; one patient developed grade 2 and 3 patients, grade 3–4 acute GVHD. Four of 13 recipients of HLA-matched sibling donor HCT developed grade 2–4 acute GVHD; two patients developed grade 2 and the remaining two patients, grade 3–4 acute GVHD. Three of 13 recipients of HLA-matched sibling and five of 12 recipients of unrelated donor HCT developed chronic GVHD. One recipient of an alternative related donor HCT developed chronic GVHD; only four patients lived beyond 90 days after HCT in this group.

Overall survival

The 5-year probability of overall survival is 62% (95% CI 44–76). Table 2 shows survival and disease status of patients after transplantation by disease status pre-transplant and donor type. Twenty-two patients are alive and 21 are in hematologic remission with performance scores $>90\%$. One patient is alive, 10 years after HCT with recurrent disease (presence of leukocyte granules 7.4 months after transplantation) but without symptoms of accelerated phase. One of the patients in remission from CHS developed myelodysplastic syndrome. She received a second allogeneic transplant 4 years after the first transplant and remains free of both diseases, 9 years from the first transplant and 5 years from the second.

Data on donor–recipient chimerism were available for 13 of 22 surviving patients. Of these, 10 patients are reported to have 100% donor chimerism. The remaining three patients have 92, 70 and 15% donor chimerism. Only the

Table 2 Transplant outcome by disease status before transplantation and donor type

Patient	*Disease status at transplantation*	*Donor*[a]	*Disease status after transplantation*	*Status*
1444	Not in accelerated phase	HLA-matched sibling	Remission	Alive, 43 mo
1763	Not in accelerated phase	HLA-matched sibling	Remission	Alive, 174 mo
15 249	Not in accelerated phase	HLA-matched sibling	Remission	Alive, 74 mo
15 273	Not in accelerated phase	HLA-matched sibling	Remission	Alive, 110 mo
18 948	Not in accelerated phase	HLA-matched sibling	Remission	Alive, 62 mo
18 956	Unknown	HLA-matched sibling	Remission	Dead, 1.5 mo
20 251	Not in accelerated phase	HLA-matched sibling	Remission	Alive, 82 mo
21 715	Accelerated phase	HLA-matched sibling	Remission	Alive, 95 mo
21 716	Accelerated phase	HLA-matched sibling	Remission	Alive, 14 mo
22 065	Not in accelerated phase	HLA-matched sibling	Remission	Alive, 31 mo
22 066	Not in accelerated phase	HLA-matched sibling	Remission	Alive, 80 mo
22 094	Accelerated phase	HLA-matched sibling	Remission	Dead, 24 mo
22 282	Not in accelerated phase	HLA-matched sibling	Remission	Alive, 57 mo
2683	Accelerated phase	Other related donor	Recurrent disease	Dead, 2.4 mo
3437	Accelerated phase	Other related donor	Recurrent disease	Dead, 1.9 mo
6074	Accelerated phase	Other related donor	Recurrent disease	Dead, 2.7 mo
13 065	Accelerated phase	Other related donor	Recurrent disease	Dead, 1.2 mo
15 103	Not in accelerated phase	Other related donor	Recurrent disease	Dead, 33 mo
15 196	Accelerated phase	Other related donor	Recurrent disease	Alive, 118 mo
18 916	Not in accelerated phase	Other related donor	Remission	Alive, 19 mo
18 982	Accelerated phase	Other related donor	Recurrent disease	Dead, 2.2 mo
19 028	Not in accelerated phase	Other related donor	Remission	Alive, 85 mo
22 317	Accelerated phase	Other related donor	Recurrent disease	Dead, 2.3 mo
7793	Not in accelerated phase	Unrelated donor	Remission	Alive, 145 mo
12 521	Not in accelerated phase	Unrelated donor	Remission	Alive, 108 mo
18 974	Not in accelerated phase	Unrelated donor	Remission	Alive, 24 mo
20 252	Not in accelerated phase	Unrelated donor	Remission	Dead, 1.3 mo
20 588	Not in accelerated phase	Unrelated donor	Remission	Alive, 61 mo
21 848	Not in accelerated phase	Unrelated donor	Remission	Alive, 62 mo
22 316	Not in accelerated phase	Unrelated donor	Remission	Alive, 98 mo
22 317	Accelerated phase	Unrelated donor	Remission	Alive, 78 mo
45 115	Unknown	Unrelated donor	Remission	Dead, 3.6 mo
46 081	Not in accelerated phase	Unrelated donor	Remission	Alive, 126 mo
46 251	Unknown	Unrelated donor	Remission	Dead, 3.2 mo
47 052	Not in accelerated phase	Unrelated donor	Remission	Dead, 7.5 mo

Abbreviations: HLA = human leukocyte antigen; mo = months.
[a]All recipients received bone marrow grafts except patient 18916 who received peripheral blood.

patient with 15% donor chimerism has clinical evidence of recurrent disease as demonstrated by the presence of leukocyte granules.

Causes of death

Overall, 13 patients died after HCT from either persistent disease or a transplant-related complication. Nine patients died within 100 days of transplantation (early mortality). Of these, six received allografts from an alternative related donor, one from an HLA-matched sibling, and the remaining two, from an unrelated donor. Causes of early mortality included: persistent disease ($n=6$) in recipients of alternative related donor HCT, adenoviral infection ($n=1$) and adult respiratory distress syndrome ($n=1$) in recipients of unrelated donor HCT, and veno-occlusive disease ($n=1$) after an HLA-matched sibling donor HCT. Causes of late mortality (>100 days) included persistent disease ($n=1$) after an alternative related donor HCT, systemic fungal infection ($n=1$) and idiopathic interstitial pneumonitis ($n=1$) after unrelated donor HSCT and chronic GVHD ($n=1$) after an HLA-matched sibling donor HCT.

Discussion

We describe outcomes after allogeneic transplantation for 35 patients with CHS. In general, these data suggest allogeneic transplantation from an HLA-matched sibling or an unrelated donor may be an effective treatment for hematologic and immunologic correction of CHS, and a history of symptoms of accelerated phase does not preclude a successful outcome. Survival after alternative related donor HCT was poor. This may be explained by the presence of symptoms of accelerated phase at transplantation in most of these recipients. The absence of symptoms of accelerated phase at transplant appears to predict fewer recurrences.

A recent retrospective review of transplantation for CHS indicates a high rate of neurocognitive sequelae in patients who have survived into their third decade after HCT.[19] A number of the patients in that series had mixed chimerism post HCT. It is not known to what extent the experience of the accelerated phase before HCT contributes to later neurocognitive deficits, and, conversely, whether HCT at a younger age could reduce or delay later neurologic deterioration. The occurrence of mild central or peripheral neuropathy in this series cannot be excluded, despite reports of excellent performance scores in the survivors and is a limitation of any registry-based study. Further, ours is a relatively young cohort, the median age of surviving patients is 12 years and the two oldest patients are 21 years of age.

Although data on donor–recipient chimerism were available for only 76% of surviving patients the data suggest that in the majority of patients long-term engraftment is durable. In those with mixed donor–recipient chimerism, only one patient has clinical evidence of recurrent disease as evidenced by the presence of leukocyte granules (15% donor chimerism). Importantly, this patient has maintained a low level of donor chimerism for almost 10 years and without symptoms of the accelerated phase of this disease.

Early mortality after transplantation was high with most deaths (nine of 13) occurring within 100 days after transplantation. Persistent disease was the most common cause of early mortality and occurred in patients transplanted in accelerated phase. Although GVHD was more frequent after unrelated donor transplantation this did not affect mortality. Although the study period spans over two decades, we did not observe differences in overall survival by year of transplantation. Our inability to detect differences in survival outcomes may be explained by the small cohort and over half of the deaths were due to recurrent disease occurring in patients with active disease at transplantation.

The current report has several limitations: small sample size, lack of detailed information on immune reconstitution and post-transplant extrahematopoietic manifestations such as neurological outcomes. Nevertheless, the data suggest HLA-matched and unrelated donor HCT with a myeloablative preparatory regimen offer a cure for an otherwise lethal disease. The poor outcome associated with accelerated phase disease at transplantation warrant confirmation in a larger study. Future studies of HCT treatment for CHS, as with other hemophagocytic disorders, should build in longitudinal neurocognitive monitoring as well as examine the role of alternative related donor HCT in patients without active disease at transplantation.

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References

1 Barak Y, Nir E. Chediak–Higashi syndrome. *Am J Pediatr Hematol Oncol* 1987; **9**: 42–55.
2 Pettit RE, Berdal KG. Chediak–Higashi syndrome. Neurologic appearance. *Arch Neurol* 1984; **41**: 1001–1002.
3 Grossi CE, Crist WM, Abo T, Velardi A, Cooper MD. Expression of the Chediak–Higashi lysosomal abnormality in human peripheral blood lymphocyte subpopulations. *Blood* 1985; **65**: 837–844.
4 Certain S, Barrat F, Pastural E, Le Deist F, Goyo-Rivas J, Jabado N *et al*. Protein truncation test of LYST reveals heterogenous mutations in patients with Chediak–Higashi syndrome. *Blood* 2000; **95**: 979–983.
5 Zarzour W, Kleta R, Frangoul H, Suwannarat P, Jeong A, Kim SY *et al*. Two novel CHS1 (LYST) mutations: clinical correlations in an infant with Chediak–Higashi syndrome. *Mol Genet Metab* 2005; **85**: 125–132.
6 Davis WC, Douglas SD. Defective granule formation and function in the Chediak–Higashi syndrome in man and animals. *Semin Hematol* 1972; **9**: 431–450.
7 Abo T, Roder JC, Abo W, Cooper MD, Balch CM. Natural killer (HNK-1+) cells in Chediak–Higashi patients are present

in normal numbers but are abnormal in function and morphology. *J Clin Invest* 1982; **70**: 193–197.
8 Rubin CM, Burke BA, McKenna RW, McClain KL, White JG, Nesbit ME *et al*. The accelerated phase of Chediak–Higashi syndrome. An expression of the virus-associated hemophagocytic syndrome? *Cancer* 1985; **56**: 524–530.
9 Aslan Y, Erduran E, Gedik Y, Mocan H, Yildiran A. The role of high dose methylprednisolone and splenectomy in the accelerated phase of Chediak–Higashi syndrome. *Acta Haematol* 1996; **96**: 105–107.
10 Fukuda M, Morimoto T, Ishida Y, Suzuki Y, Murakami Y, Kida K *et al*. Improvement of peripheral neuropathy with oral prednisolone in Chediak–Higashi syndrome. *Eur J Pediatr* 2000; **159**: 300–301.
11 Filipovich AH, Shapiro RS, Ramsay NK, Kim T, Blazar B, Kersey J *et al*. Unrelated donor bone marrow transplantation for correction of lethal congenital immunodeficiencies. *Blood* 1992; **80**: 270–276.
12 Fischer A, Landais P, Friedrich W, Gerritsen B, Fasth A, Porta F *et al*. Bone marrow transplantation (BMT) in Europe for primary immunodeficiencies other than severe combined immunodeficiency: a report from the European Group for BMT and the European Group for Immunodeficiency. *Blood* 1994; **83**: 1149–1154.
13 Diamond HR, Souza MH, Silva ML, Tabak DG, Ferman S, M-Silva VM *et al*. Natural killer cell activity in a patient with Chediak–Higashi syndrome submitted to bone marrow transplantation. *Pediatr Hematol Oncol* 1995; **12**: 399–402.
14 Mottonen M, Lanning M, Saarinen UM. Allogeneic bone marrow transplantation in Chediak–Higashi syndrome. *Pediatr Hematol Oncol* 1995; **12**: 55–59.
15 Haddad E, Le Deist F, Blanche S, Benkerrou M, Rohrlich P, Vilmer E *et al*. Treatment of Chediak–Higashi syndrome by allogenic bone marrow transplantation: report of 10 cases. *Blood* 1995; **85**: 3328–3333.
16 Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J *et al*. 1994 Consensus conference on acute GVHD grading. *Bone Marrow Transplant* 1995; **15**: 825–828.
17 Flowers ME, Kansu E, Sullivan KM. Pathophysiology and treatment of graft-versus-host disease. *Hematol Oncol Clin North Am* 1999; **13**: 1091–1112, viii-ix.
18 Klein JP, Moeschberger ML. *Survival Analysis: Techniques of Censored and Truncated Data*. Springer-Verlag: Berlin, 2003.
19 Tardieu M, Lacroix C, Neven B, Bordigoni P, de Saint Basile G, Blanche S *et al*. Progressive neurologic dysfunctions 20 years after allogeneic bone marrow transplantation for Chediak–Higashi syndrome. *Blood* 2005; **106**: 40–42.