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Long-term outcomes of 176 patients with X-linked hyper-IgM syndrome treated with or without hematopoietic cell transplantation

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Abstract

Background—X-linked hyper-IgM syndrome (XHIGM) is a primary immunodeficiency with high morbidity and mortality compared with those seen in healthy subjects. Hematopoietic cell transplantation (HCT) has been considered a curative therapy, but the procedure has inherent complications and might not be available for all patients.

Objectives—We sought to collect data on the clinical presentation, treatment, and follow-up of a large sample of patients with XHIGM to (1) compare long-term overall survival and general well-being of patients treated with or without HCT along with clinical factors associated with mortality and (2) summarize clinical practice and risk factors in the subgroup of patients treated with HCT.

Methods—Physicians caring for patients with primary immunodeficiency diseases were identified through the Jeffrey Modell Foundation, United States Immunodeficiency Network, Latin American Society for Immunodeficiency, and Primary Immune Deficiency Treatment Consortium. Data were collected with a Research Electronic Data Capture Web application. Survival from time

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of diagnosis or transplantation was estimated by using the Kaplan-Meier method compared with log-rank tests and modeled by using proportional hazards regression.

Results—Twenty-eight clinical sites provided data on 189 patients given a diagnosis of XHIGM between 1964 and 2013; 176 had valid follow-up and vital status information. Sixty-seven (38%) patients received HCT. The average follow-up time was 8.5 ± 7.2 years (range, 0.1–36.2 years). No difference in overall survival was observed between patients treated with or without HCT ($P = .671$). However, risk associated with HCT decreased for diagnosis years 1987–1995; the hazard ratio was significantly less than 1 for diagnosis years 1995–1999. Liver disease was a significant predictor of overall survival (hazard ratio, 4.9; 95% confidence limits, 2.2–10.8; $P < .001$). Among survivors, those treated with HCT had higher median Karnofsky/Lansky scores than those treated without HCT ($P < .001$). Among patients receiving HCT, 27 (40%) had graft-versus-host disease, and most deaths occurred within 1 year of transplantation.

Conclusion—No difference in survival was observed between patients treated with or without HCT across all diagnosis years (1964–2013). However, survivors treated with HCT experienced somewhat greater well-being, and hazards associated with HCT decreased, reaching levels of significantly less risk in the late 1990s. Among patients treated with HCT, treatment at an early age is associated with improved survival. Optimism remains guarded as additional evidence accumulates.

Keywords

X-linked hyper-IgM syndrome; CD40 ligand; hematopoietic cell transplantation; defects in class-switch recombination; long-term outcomes; primary immunodeficiency; Karnofsky/Lansky scores

X-linked hyper-IgM syndrome (XHIGM; OMIM #308230) is a primary immunodeficiency with an estimated prevalence in the United States of 1:1,000,000.¹ Initially described as “dysgamma-globulinemia” because patients had recurrent infections associated with low or absent levels of IgG and increased levels of IgM,^{2,3} the molecular defect is the result of mutations in the CD40 ligand (*CD40LG*) gene.^{4–14} Binding of CD40 ligand, which is expressed by activated CD4⁺ T cells, to its receptor CD40, which is constitutively expressed by B cells, is critical for immunoglobulin isotype switching and an effective secondary antibody response. CD40 ligand binding to CD40 expressed on dendritic cells and macrophages leads to their maturation, activation, and cytokine secretion, which contribute to an effective T-cell response. This dual function explains the combined nature of the immunodeficiency.^{15–20}

For the past 2 decades, retrospective series have reported on the clinical characteristics of patients with XHIGM. The spectrum of disease includes recurrent bacterial infections occurring early in life; opportunistic infections caused by *Pneumocystis jirovecii* are frequently the presenting feature, and infection with *Cryptosporidium* species is a presumed contributor to sclerosing cholangitis and hepatic/bile duct malignancies. In more than 50% of cases, chronic or intermittent neutropenia is recognized; parvovirus-induced red cell aplasia and progressive neurodegeneration of unknown cause have also been reported.^{21,22} The overall prognosis is poor, with an average of 20% survival by age 25 years.^{1,23–27}

Because the reported morbidity and mortality in patients with XHIGM is high compared with those in healthy subjects, hematopoietic cell transplantation (HCT) has been considered a potential curative therapy for some time. Reports of successful HCT have been accumulating, with increasing numbers of patients undergoing this procedure.^{1,28–41} Recently, Mitsui-Sekinaka et al⁴² compared long-term outcomes of 29 patients undergoing transplantation with those of 27 patients treated with conventional medical therapies and concluded that HCT improved the outcomes of patients with XHIGM.

Given the inherent complications with HCT (particularly if a fully matched sibling donor is not available) coupled with the anecdotal observations of long-term survival without HCT, updated outcome data are needed to determine optimal XHIGM management. Current approaches include immunoglobulin replacement therapy; antimicrobial prophylaxis for opportunistic infections; close monitoring for complications, such as neutropenia and liver disease; and careful precautions to avoid *Cryptosporidium* species exposure. Importantly, prognostically useful clinical or laboratory variables are not well established to help guide therapeutic choices.

This retrospective analysis of a large international cohort sought to collect data on the clinical presentation, treatment, and follow-up of a large sample of patients with XHIGM and use this information to (1) compare long-term overall survival and general well-being of patients treated with or without HCT and clinical factors associated with mortality and (2) summarize clinical practice and risk factors in the subgroup of patients treated with HCT.

METHODS

This study is retrospective, observational, and multinational. Physicians caring for patients with primary immunodeficiency diseases (PIDs) were identified through the Jeffrey Modell Foundation, United States Immunodeficiency Network, Latin American Society for Immunodeficiency, and Primary Immune Deficiency Treatment Consortium. The European Society for Immunodeficiency published an announcement for this study in the European Society for Immunodeficiency newsletter Web site. An e-mail requesting participation in a survey was sent to 183 physicians. Survey data were collected under an approved institutional review board protocol titled “A natural history study of long term outcomes of patients with X-linked hyper IgM syndrome” and managed by using Research Electronic Data Capture (REDCap) hosted at UT Southwestern Medical Center Dallas.⁴³ A total of 106 fields were compiled and divided into 4 sections: (1) demographics (institution and country of origin), age at diagnosis, year of diagnosis, family history of XHIGM, vital status (alive or deceased), and age at last follow-up; (2) mutation in *CD40LG* (previously published mutations were provided as annotated in <http://bioinf.uta.fi/CD40Lbase/>); (3) HCT treatment, including age and year of transplantation, relationship of donor, source of stem cells, conditioning regimen, engraftment, and evidence of graft-versus-host disease (GVHD), for those patients undergoing more than 1 HCT (the same questions were asked for each subsequent HCT); and (4) clinical presentation, postdiagnosis treatment, and Karnofsky/Lansky scores at last follow-up. For the complete survey instrument, see the REDCap survey included in this article’s Online Repository at www.jacionline.org.

The study was designed for a target enrollment of 200 subjects and assumed an HCT prevalence of 40%. Sample sizes in the range 165 to 200 provide 80% power to detect an overall hazard ratio of 1.8 or greater between patients treated with or without HCT. Characteristics of patients at the time of diagnosis were summarized along with their ensuing medical management. Postdiagnosis survival was estimated by using the Kaplan-Meier method, and log-rank tests were used to compare survival. Proportional hazards regression of postdiagnosis survival was used to estimate a hazard ratio for treatment with versus without HCT that varied smoothly and continuously with diagnosis year. A cubic regression spline of diagnosis year was used for this purpose. Clinical factors simultaneously associated with postdiagnosis survival were explored by using proportional hazards regression on a candidate pool of predictors, including respiratory tract involvement, hematologic involvement, gastrointestinal disease, liver/biliary involvement, central nervous system involvement, failure to thrive, malignancy, and history of infection by *P. jirovecii* pneumonia, mycobacteria, BCG infection, parvovirus, cytomegalovirus, or *Cryptosporidium* species. Additionally, in the subgroup of HCT recipients, characteristics were summarized at the time of HCT, and log-rank tests were used to assess posttransplantation risk of HCT donor relationship, source of hematopoietic cells (bone marrow, umbilical cord, or peripheral blood cells), age at HCT, year of HCT, and conditioning regimen. Timeline plots were created to show individual follow-up times from diagnosis for all patients and those in the HCT subgroup. All analyses were programmed in SAS/STAT software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Recruitment and characteristics of the sample

A total of 189 subjects from 28 clinical sites were entered in REDCap from August 2012 to September 2013. Forty-seven of 183 physicians contacted provided data. To achieve adequate statistical power for analysis, patients with definitive (documented mutation in *CD40LG*) or probable/possible diagnosis of XHIGM based on male sex, X-linked inheritance, or clinical presentation, as diagnosed by participating physicians, were included; 13 (7%) subjects were excluded because of invalid follow-up time or vital status information, allowing analysis of 176 total patients.

The geographic distribution of patients is shown in Fig 1. The sample included 88 (50%) patients from North America (Canada and the United States); 51 (29%) patients from European countries (Belgium, Croatia, the Czech Republic, Germany, Greece, the Netherlands, Russia, Serbia, Spain, and the United Kingdom); 25 (14%) patients from South America (Argentina and Brazil); and 12 (7%) patients from Iran, Turkey, and Australia.

Characteristics of the patients are summarized in Table I. The median year of XHIGM diagnosis for the entire cohort was 2002 (range, 1964–2013). Molecular diagnosis was available for 135 (77%) patients. The median age at diagnosis was 1 year (range, birth to 59.3 years). Twenty-nine patients received a diagnosis before 1993, the year the *CD40LG* gene was cloned. In 17 of these patients, a family history indicative of X-linked inheritance was reported, and a mutation in *CD40LG* was confirmed in 14 of them (data not shown).

The median age at last follow-up was 11 years (range, 0.1–60.7 years), and the mean follow-up time after establishing the diagnosis was 8.5 ± 7.2 years (range, 0.1–36.2 years).

Clinical management is shown in Table II. Immunoglobulin replacement and *P jirovecii* prophylaxis were reported for 95% and 75% of patients, respectively. Forty-five percent of patients with neutropenia were treated with rhG-CSF, whereas azithromycin prophylaxis was used in only 8%. No statistical differences in these practices were observed based on country of origin, except for transplantation practice ($P < .001$, Fig 1 and Table II): European patients (26/51 [51%]) were more likely to have undergone HCT compared with patients from North America (36/88 [41%]) or those from South America (5/25 [20%]), although 14 (54%) of 26 transplantations in European patients were performed at a single site.

Comparison of long-term overall survival and general well-being of patients treated with or without HCT

The primary objective of the study was to compare the postdiagnosis survival of patients with XHIGM treated with or without HCT. The median survival time from diagnosis was 25 years for all patients (Fig 2, A). No difference in overall survival was noted when patients were stratified by the year in which the diagnosis of XHIGM was made ($P = .298$; see Fig E1 in this article's Online Repository at www.jacionline.org). The transplant group appears to fare better during the first 12 years after diagnosis; however, overall survival between patients treated with or without HCT did not differ ($P = .671$; Fig 2, B). The median survival time from diagnosis was similar between the 2 groups (25 years without HCT vs 20 years with HCT; Fig 2, B). These data were confirmed in the subgroup of patients with a known mutation in *CD40LG* (see Figs E2 and E3 in this article's Online Repository at www.jacionline.org). No difference in survival was noted when birth was used as time 0 for the Kaplan-Meier analysis (see Fig E4 in this article's Online Repository at www.jacionline.org).

The study was powered to detect a hazard ratio of 1.8 or greater between patients treated with or without HCT aggregated over all diagnosis years (1964–2013). Given changes in HCT practice over the past 4 decades, we explored the possibility that the hazard ratio might have also changed over time. Fig 3 shows the hazard ratio for treatment with versus without HCT as a function of diagnostic year, including all years with at least 5 preceding and subsequent deaths. The hazard associated with HCT decreased for diagnosis years 1987–1995; the hazard ratio was significantly less than 1 for diagnosis years 1995–1999. For earlier or later diagnosis years, the widening confidence band reflects the reduced sample size and/or follow-up time and consequent loss of power.

At the close of the survey, 144 patients were living: 57 (85%) of 67 of those treated with HCT and 87 (80%) of 109 of those treated without HCT. Those treated with HCT had higher median Karnofsky/Lansky age performance scores than those treated without HCT (100.0% with HCT vs 90.0% without HCT, $P < .001$; Fig 4).

Clinical factors associated with mortality

Affected organ system involvement at the time of diagnosis is depicted in Tables E1 and E2 in this article's Online Repository at www.jacionline.org. Documented infections were

recognized in 80% of patients; in almost half of these (43% [61/176]), *P jirovecii* was the presenting manifestation (data not shown), and it was common for patients to have had more than 1 organ affected. Thirty-six (36/176 [20%]) patients were found to have liver disease, which was the presenting manifestation of XHIGM in more than 40% (16/36) of these cases. Although *Cryptosporidium* species was not frequently identified among the whole cohort (13/176 [7%]), it was noted in 25% (8/36) of patients with associated liver disease. There was no trend in the identification of this pathogen over time because it was observed in patients who had been given a diagnosis of XHIGM between 1987 and 2012. Three patients underwent liver transplantation, and 2 also received HCT; both of these patients are alive with a Karnofsky score of 90%. The third patient was given a diagnosis of sclerosing cholangitis at age 33 years and XHIGM at age 36 years and underwent liver transplantation at age 38 years, dying shortly thereafter of complications of liver transplantation (data not shown).

Liver/biliary involvement was identified as the only significant negative predictor of survival from diagnosis (hazard ratio, 4.9; 95% confidence limit, 2.2–10.8; $P < .001$) by using best subset selection of clinical predictors at presentation in the proportional hazards model. The corresponding survival estimates are shown in Fig 5. In addition to liver/biliary involvement, the candidate pool of predictors at the time of diagnosis included respiratory tract involvement, hematologic involvement, gastrointestinal disease, central nervous system involvement, failure to thrive, malignancy, and history of infection with *P jirovecii* pneumonia, mycobacteria, BCG infection, parvovirus, cytomegalovirus, or *Cryptosporidium* species.

A total of 8 (4.5%) of 176 patients had a malignancy, which was associated with high mortality (6/8 [75%], Table III). Malignancy diagnosis ranged from before XHIGM diagnosis (patient 206) to 25 years after diagnosis (patient 24). Only 1 patient had evidence of *Cryptosporidium* species. All patients with tumors involving the bile ducts died.

Among decedents, the cause of death for patients not undergoing HCT and transplanted patients is noted in Table IV. Malignancy as a cause of death was only noted for patients without HCT (Tables III and IV).

Clinical practice and risk factors in the subgroup of patients treated with HCT

Sixty-seven (38%) patients received HCT. When patients undergoing HCT were compared with those treated without HCT (Table I), no difference was noted between the 2 groups for year of diagnosis (without HCT: median of 2001 [range, 1964–2013] vs HCT: median of 2003 [range, 1978–2012]; $P = .638$) and total follow-up time (without HCT: mean of 8.7 ± 7.7 years vs HCT: mean of 8.2 ± 6.4 years, $P = .866$). Of 8 patients given a diagnosis at birth, 4 underwent transplantation.

Patients treated with HCT were less likely to have an established molecular diagnosis (60% with HCT vs 87% without HCT, $P < .001$), were younger at the time of diagnosis (median age, 0.6 years with HCT versus 1.6 years without HCT; $P < .001$), were less likely to have a family history of XHIGM (34% with HCT vs 50% without HCT, $P = .029$), and were

younger at last follow-up (median age, 8 years with HCT vs 13 years without HCT; $P = .001$).

Transplant-related characteristics are outlined in Table E3 in this article's Online Repository at www.jacionline.org. Excluding subjects for whom conditioning data were not provided, 93% of myeloablated patients engrafted, and 85% of nonmyeloablated patients engrafted ($P = .384$, Fisher exact test). Forty percent (27/67) had GVHD, most reported as acute (20/27 patients). Nine (13%) patients underwent a second HCT (7 of these had received myeloablative conditioning, and 2 were reported as nonmyeloablated), and 1 received a total of 3 HCT transplants (data not shown).

Although patients treated with HCT were given a diagnosis of XHIGM between 1978 and 2012, transplants were performed between 1996 and 2012. The median age at transplantation was 2.9 years (range, 0.1–24 years). The median time between diagnosis and transplantation was 1.8 years (range, 30 days–23.25 years), and the mean follow-up time after transplantation was 8.1 ± 6.4 years (range, 0.1–35.3 years). Posttransplantation survival was estimated at greater than 80% at 10 years. Most deaths occurred within 1 year of transplantation (Fig 6, A). Given changes in transplantation practices, we evaluated if 1-year survival has improved in the past 2 decades. We compared the first 10 years of transplantation practices to the following 8 years. That is, 2 transplant year intervals were defined: 1996–2005 and 2006–2013. The survival plot is shown in Fig E5 in this article's Online Repository at www.jacionline.org. One-year survival is approximately 80% in the earlier group and close to 90% in the later transplant group ($P = .057$). However, at the end of 2 years, only 13 patients remain in the later transplant group, and follow up is limited. Transplant survival was statistically different for patients receiving a diagnosis before 1993 ($P < .001$; Fig 6, B). In contrast, no difference in overall survival was found from the time of diagnosis for all patients, including those with a known mutation in *CD40LG* and when stratified by whether they received an HCT. Although not statistically significant, lower risk for HCT is noted in more contemporary cohorts (ie, those patients with a *CD40LG* mutation and receiving a diagnosis after 1993; $n = 112$; see Figs E6 and E7 in this article's Online Repository at www.jacionline.org).

Several transplantation variables were explored as to whether they predicted survival: age at transplantation predicted survival, reaching statistical significance at increased age (Fig 6, C–F). Year of HCT, donor relationship, hematopoietic stem cell source, conditioning regimen, engraftment, or GVHD did not influence survival ($P > .286$, log-rank test; see Fig E8, A–F, in this article's Online Repository at www.jacionline.org). Liver disease at the time of transplantation was a predictor of poor outcome within the transplant group (see Fig E9 in this article's Online Repository at www.jacionline.org).

For those patients undergoing transplantation, the cause of death is noted in Table IV. Infections and transplant-related complications were the principle cause of death. HCT-related complications included veno-occlusive disease and GVHD: patient 58 received a nonmyeloablative conditioning, and patients 63 and 105 received myeloablative therapy (Table IV).

Timeline plots for postdiagnosis survival of patients with XHIGM with HCT intervals are noted in Fig E10 in this article's Online Repository at www.jacionline.org. Most patients undergoing HCT have a short follow-up time after transplantation, with most less than 5 years, even in patients with fairly long total follow-up times from diagnosis. Within this HCT subgroup, there are only 5 deaths in timelines longer than 10 years after diagnosis, 4 of these less than a year after transplantation.

DISCUSSION

We report the results of an international, collaborative, retrospective survey on the outcome of patients with XHIGM, which includes 176 patients and represents the largest group of patients with XHIGM with valid follow-up time and vital status information reported to date. To ensure patients without a genetic confirmation represented XHIGM and did not influence the results, all survival analysis for any queried variable was performed both in the whole patient cohort and after separating those with (n =135) or without (n =41) a molecular diagnosis in *CD40LG*. The lack of confirmation of a genetic defect did not affect the results.

The morbidity and mortality associated with XHIGM have resulted in treatment recommendations that focus on the prevention of infections, and the only proposed curative therapy is HCT.²⁷ Although geographic differences were noted in HCT practices, no significant difference in geographic practices was noted for prophylactic therapies. Yet in this series 5% of patients were not treated with gammaglobulin therapy; 25% were not receiving prophylaxis for *P. jirovecii*, including 16% of patients in whom *Pneumocystis* species was the presenting clinical manifestation; and less than 50% of patients with neutropenia were treated with rhG-CSF, suggesting subtle differences in clinical care (Tables I and II).

One hundred forty-four (81.8%) patients were alive at closure of enrollment, ranging in age from 1 month to 60.7 years. The oldest survivor was 60.7 years old, had not undergone transplantation, and was the oldest amongst all patients at last follow-up. The mortality rate of 2.2% per year, representing 18.2% of deaths in this series of patients, is higher than previously reported in the US series of 79 patients (10.1%)¹ but lower when compared with the European study (23.2%) performed 20 years ago.²⁷ The overall survival for patients remains guarded, with a median survival of 25 years from the time of diagnosis (Fig 2, A). This is similar to the findings of a recent 14-year (1998–2012) retrospective analysis of 56 Japanese patients with XHIGM, in which overall mortality was high at 32% with a median survival of 23 years.⁴²

The primary aim of the study was to compare long-term survival of patients with XHIGM treated with or without HCT. We chose to perform postdiagnosis survival estimates, as done with the Kaplan-Meier method. Using birth as time 0 provides homogeneity and comparable start times for all subjects. However, in clinical practice it is rare for patients to come to medical attention at birth, often despite a family history. This was noted not only in our cohort of patients (Table I) but also in other groups of patients with PIDs in whom an X-linked pattern of inheritance is well established.⁴⁴ In our study no difference in survival was observed between patients treated with or without HCT across all diagnosis years (1964–

2013; Fig 2, B). This is in contrast to the Japanese experience.⁴² However, in the latter study there were no early deaths in the transplant group, and it is possible that these results were confounded if patients who do not survive to receive a transplant were included as non-transplant-related deaths. The analysis represented in Fig 2, A and B, conveys the message that cumulative survival decreases steadily with time from diagnosis. Of note, because few patients are followed beyond 10 years, when deaths do occur after this time, they have a greater effect on the estimated survival probability because of the decreased numbers remaining at risk.

Expanding on this idea, a timeline plot was created that demonstrates follow-up times from diagnosis for each patient (see Fig E10). Among the HCT subgroup, 5 deaths occurred 10 years after diagnosis, 4 of these less than a year after transplantation. The length of follow-up is certainly a limitation of the study. It is possible that if the length of follow-up were longer (ie, into the fourth, fifth, and sixth decades of life), the Kaplan-Meier curves could diverge in favor of transplantation.

Furthermore, recognizing that transplant practices have improved in the past 4 decades (better HLA typing methods, better antifungal, and viral monitoring), we sought to evaluate whether this observation could have influenced survival. Indeed, a survival benefit for the transplant group was gradually noted after 1987, reaching statistical significance (hazard ratio, <1) in the late 1990s, when sample size, follow-up time, and power were adequate for analysis (Fig 3). Lastly, survivors treated with HCT experienced slightly better well-being, as measured by using Karnofsky/Lansky scales, than those without HCT ($P < .001$).

An important weakness of this study is the lack of longitudinal clinical data after diagnosis. For example, not captured are the numbers of infections occurring after diagnosis, hospitalizations, or missed days of school or work. These data would have provided a better indicator of what patients should expect once the diagnosis is established, despite the institution of preventative measures. A similar observation has been noted in patients with chronic granulomatous disease. When patients undergoing HCT for CGD were compared with those not undergoing transplantation and followed longitudinally, the latter group did worse, encountering more serious infections and hospitalizations, even though overall survival was fairly good through childhood years.⁴⁵

The clinical presentation at time of diagnosis is similar to that in previously reported series (see Table E1).^{1,23,27} Although almost 50% of patients had a family history of XHIGM, only 10% of these boys were given a diagnosis at birth (Table I). This is lower than previously reported.^{1,44} In this series *P jirovecii* was the presenting manifestation in 43% of patients, which is remarkably similar to data reported almost 2 decades ago.^{1,27} In contrast, only 26% of patients from the Latin America Registry present with *Pneumocystis* species infection.²⁵ Depending on pathogen exposure, other infections might dominate at the time of presentation, as demonstrated by a recent Chinese cohort in which 30% of patients came to medical attention with complications after BCG vaccination.⁴⁶ *Cryptosporidium* species is well recognized as a significant cause of morbidity and mortality in patients with XHIGM. In this series only 13 (7.4%) of 176 patients had this organism identified, which is less than initially reported from the European and North American studies.^{1,27} However,

Cryptosporidium species was identified in the majority of patients who had liver disease at presentation (13/16 [81%]). This relatively low percentage overall might reflect the difficulty of identifying the organism in stool. Newer PCR-based diagnostic methodologies for detection of *Cryptosporidium* species provides an opportunity for prospective studies to better judge the effect of this organism on survival of patients with XHIGM.

When multiple regression models were performed to identify clinical variables at presentation that predicted survival, liver disease at diagnosis was the only significant predictor of mortality and reached statistical significance for the HCT group if present at the time of transplantation (Fig 5 and see Fig E9). The clinical data on pulmonary status were not collected at the time of transplantation, and therefore we cannot comment on whether pre-existing lung diseases at the time of transplantation influenced survival, as has been previously reported.^{38,47} An important difference in mortality between patients undergoing transplantation and those not undergoing transplantation is the development of malignancy. This was only noted in the group not undergoing transplantation, and the time to such complication was reported as late as 25 years after diagnosis.

For the subgroup of patients who underwent transplantation, 85% were surviving. The overall survival is similar to that reported in the Japanese experience comprising patients from 1998–2012⁴² and improved compared with 68% overall survival from the European experience with HCT for patients with XHIGM between 1993 and 2002.⁴¹ Transplant survival was influenced by year of diagnosis and age at transplantation (Fig 6, B–F). Those patients given a diagnosis before 1993 fared worse, suggesting improvement in the care of patients with XHIGM after the genetic basis for the disease was discovered. Older age at transplantation has been recognized as a risk factor for poor outcome when patients with PIDs underwent transplantation.^{38,48,49} Similarly, in patients with XHIGM, survival worsened as the age at transplantation increased past 5 years (Fig 6, E and F). Taken together, if the decision for HCT is agreed upon, this should be done before liver disease and preferably before age 10 years (Figs 5 and 6). Nonetheless, with improvement in the care of patients with XHIGM before transplantation, betterment in transplantation outcomes could also be seen for older patients with XIGM, as observed in those with other PIDs, as long as organ damage and infections are controlled.^{50,51}

Taken together, the data presented suggest an improvement in HCT survival for patients with XHIGM receiving a diagnosis after 1993. Data collection in this survey did not include information on the characteristics of immune reconstitution, a critical aspect of our understanding of HCT as a cure for this congenital defect in immune function. In this series 12% of patients did not engraft and 40% had GVHD, underscoring the need for detailed analysis of transplant outcomes and how they affect a patient's quality of life.

Many questions remain. What standard of care prophylactic practices and surveillance should be implemented in the everyday care for these patients and how can this be measured? An analysis on the process of clinical decision making by physicians caring for patients with XHIGM provides an opportunity to evaluate how such practices can affect long-term survival. Does transplantation prevent the appearance of malignancy, an important cause of death for patients not undergoing transplantation? How are transplant related

morbidities, including graft failure and GVHD, impacting a patient's quality of life? Finally, will gene therapy and evolving recombinant technologies be better options in the future?⁵²

When caring for patients with life-limiting diseases, improving survival while optimizing quality of life are the primary goals. For patients with XHIGM, long-term survival remains guarded. For those patients who have potential HCT donors, HCT performed before the age of 10 years and before the development of liver diseases might offer not only a survival advantage but also improved long-term general well-being. For those patients who do not have the option of HCT, it is encouraging to see that long-term survival has improved in the last 4 decades. Yet furthering our understanding of risk factors that lead to liver disease and development of malignancies will be critical for their long-term survival. Multicenter longitudinal prospective studies that include quality-of-life measures are necessary to standardize best practices and identify those variables that provide patients with the best chance for a normal life.

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We respectfully dedicate this work to the memory of our colleague, coauthor, and friend Dr Trudy Small and to our patients and their families for their constant inspiration.

Abbreviations used

CD40LG	CD40 ligand
GVHD	Graft-versus-host disease
HCT	Hematopoietic cell transplantation
PID	Primary immunodeficiency disease

REDCap Research Electronic Data Capture

XHIGM X-linked hyper-IgM syndrome

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Key messages

- X-linked hyper IgM is a rare primary immunodeficiency associated with high morbidity and mortality. Prognosis remains guarded, with a median survival time from diagnosis of 25 years.
- Infections, including those caused by opportunistic pathogens, neutropenia, liver disease and malignancy are clinical manifestations that can be present at diagnosis. Of these, liver disease is a significant predictor of overall survival.
- Preventive measures including gamma-globulin therapy and antibiotic prophylaxis are commonly used, independent of the patient's global geographic location.
- Hematopoietic cell transplantation offers the only curative therapeutic option. However, this retrospective analysis showed no difference in survival between patients treated with or without transplantation. Although, measures of activity of daily living, favored transplantation.

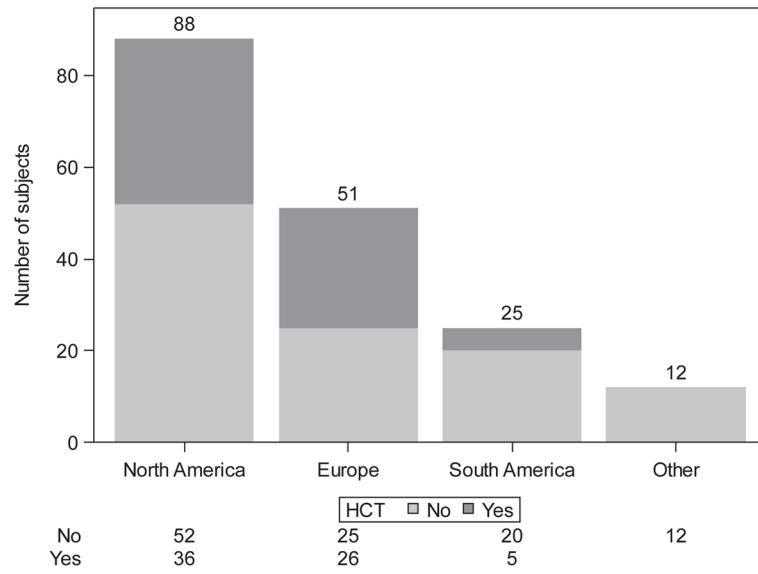
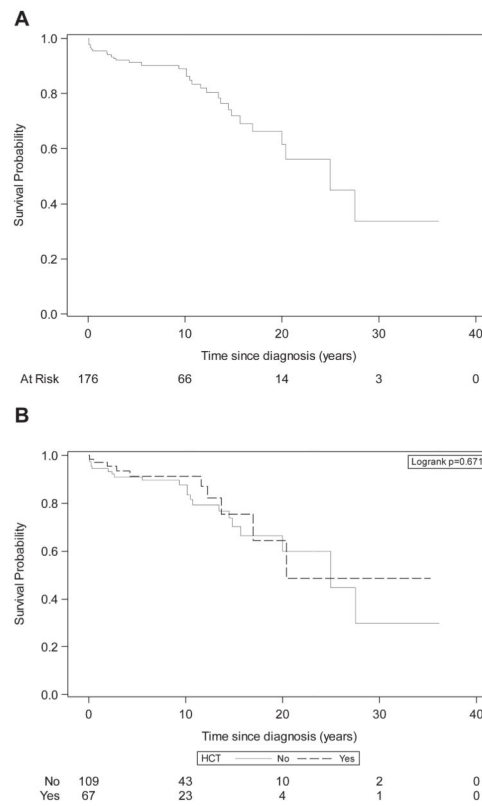


FIG 1. Geographic distribution of study subjects and HCT practices. Stacked bar graphs indicate the number of patients with XHIGM treated with (*dark bars*) or without (*light bars*) HCT.

**FIG 2.**

Kaplan-Meier estimate of postdiagnosis survival of 176 patients with XHIGM for all patients (**A**) and by HCT group (**B**). Median survival time was 25 years for all patients, and there was no statistical difference in survival probability between the HCT and non-HCT treatment groups ($P = .671$).

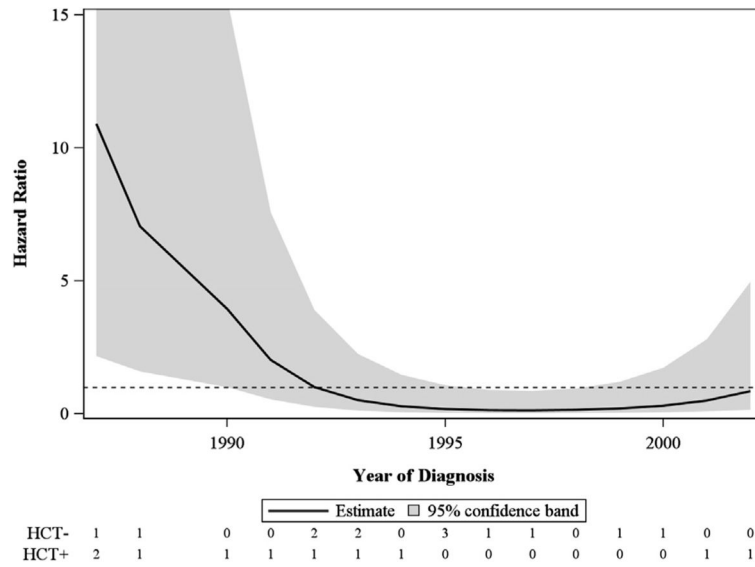


FIG 3. Estimated hazard ratio and 95% confidence band for treatment with versus without HCT in 176 patients with XHIGM, showing line of unity (*dashed*) and number of deaths by HCT group for diagnosis years with at least 5 preceding and subsequent deaths.

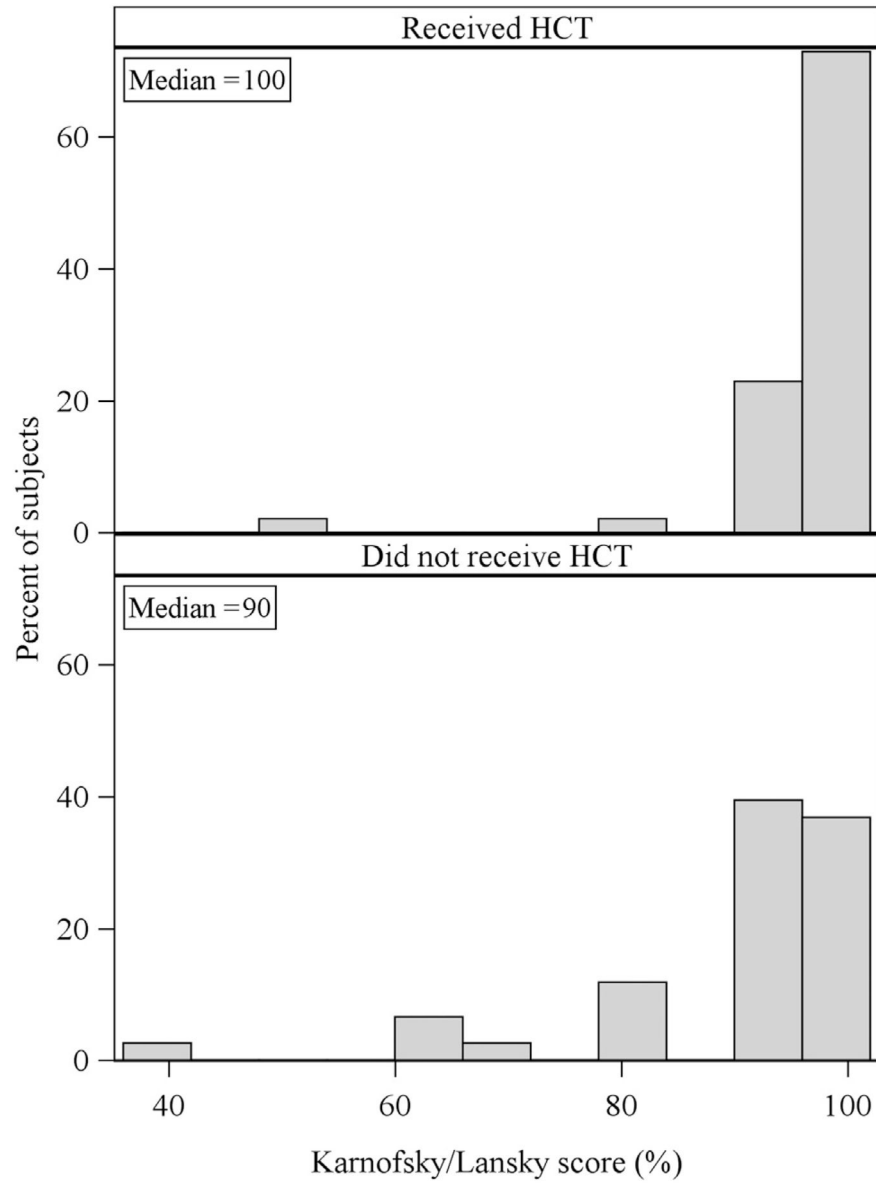


FIG 4. Karnofsky/Lansky scores (as percentages) of surviving patients with XHIGM.

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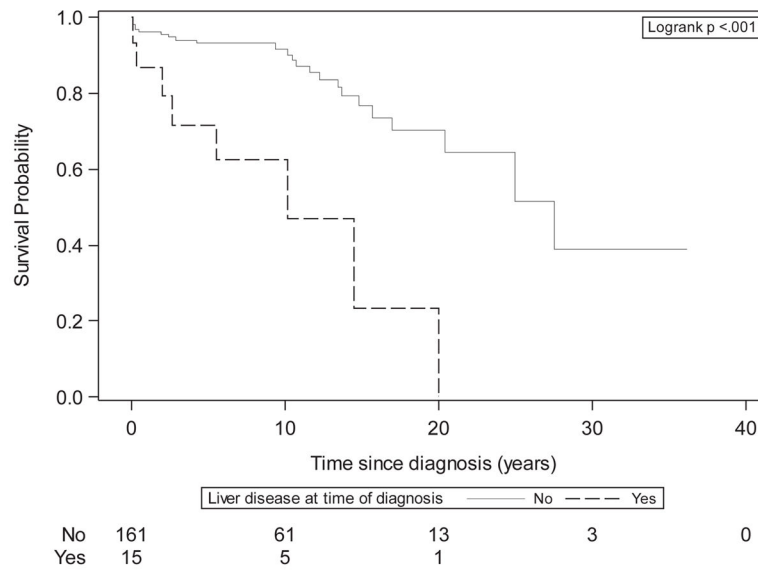


FIG 5. Kaplan-Meier estimates of postdiagnosis survival of patients with XHIGM by liver disease. Among all patients with XHIGM, liver disease at the time of diagnosis is a significant negative predictor of survival ($P < .001$).

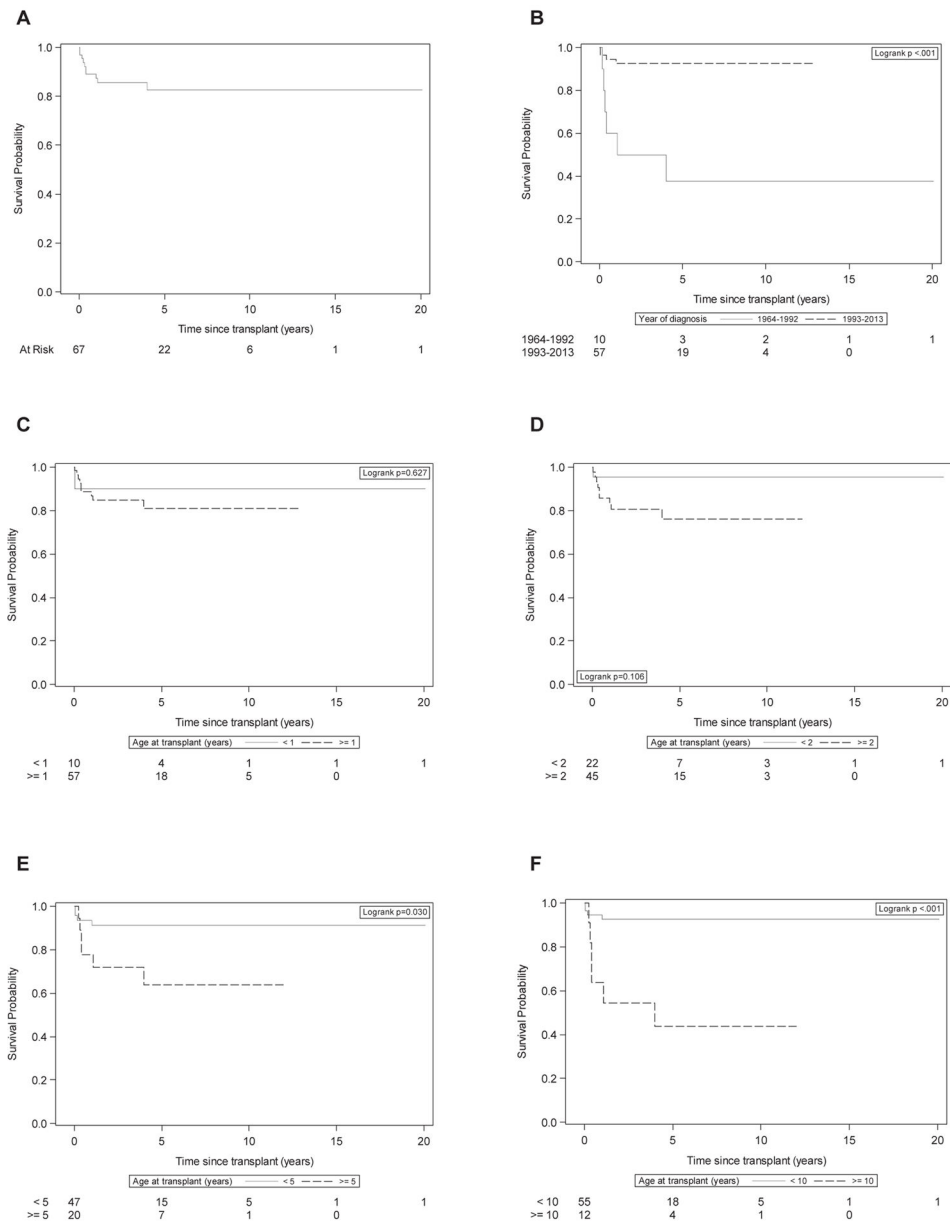


FIG 6. **A**, Kaplan-Meier estimate of posttransplantation survival of 67 patients with XHIGM treated with HCT. **B**, Kaplan-Meier estimates of posttransplantation survival by year of diagnosis: before 1993 (1964–1992) and after 1993 (1993–2013). **C–F**, Kaplan-Meier estimates of posttransplantation survival by age at transplantation: Fig 6, **C**, less than 1 year versus greater than 1 year; Fig 6, **D**, less than 2 years versus greater than 2 years; Fig 6, **E**, less than 5 years versus greater than 5 years; Fig 6, **F**, less than 10 years versus greater than 10 years.

TABLE I

Characteristics of study patients (n = 176)

	Total subjects (n = 176)	No HCT (n = 109)	HCT (n = 67)	P value*
Year of diagnosis, median (range)	2002 (1964–2013)	2001 (1964–2013)	2003 (1978–2012)	.638
Established molecular diagnosis (%)	135 (77)	95 (87)	40 (60)	<.001
Age at Diagnosis (y), median (range)	1 (0–59.3)	1.6 (0–59.3)	0.6 (0–14)	<.001
Positive family history [†] (%)	77 (44)	54 (50)	23 (34)	.029
Age at last follow-up (y), median (range)	11 (0.1–60.7)	13 (0.1–60.7)	8 (0.1–36)	.001
Total follow-up time (y), mean \pm SD (range)	8.5 \pm 7.2 (0.1–36.2)	8.7 \pm 7.7 (0.1–36.2)	8.2 \pm 6.4 (0.1–35.3)	.866

*Fisher exact tests were used for categorical variables, and Wilcoxon rank-sum tests were used for continuous and ordinal variables.

[†]Eight patients were given a diagnosis at birth (4 received no HCT and 4 underwent HCT).

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TABLE II

Characteristics of clinical practice

Clinical practice	Yes (%)	No (%)	Geographic differences in practice, <i>P</i> value*
Gamma globulin infusions started at diagnosis [†] (total n = 172)	163 (95)	9 (5)	.638
<i>Pneumocystis jirovecii</i> prophylaxis started at diagnosis ^{†§} (total n = 172)	129 (75)	43 (25)	.384
Azithromycin prophylaxis [‡] (total n = 169)	14 (8)	155 (92)	.371
rhG-CSF for neutropenia (total n = 87)	39 (45)	48 (55)	.354
HCT (total n = 176)	67 (38)	109 (62)	<.001

* Fisher exact tests for geographic differences in clinical management.

[†]No response = 4.

[‡]No response = 7.

[§]Eighty-three percent (n = 51) of patients with *Pneumocystis jirovecii* pneumonia were subsequently placed on prophylaxis.

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TABLE III

Clinical characteristics of patients with XHIGM with malignancy

Patient ID	XHIGM diagnosis age (y), year	CD40LG mutation	Type of malignancy, age at diagnosis	HCT	Clinical manifestations	Status
206	16.9, 1995	c.409+1G>A	Bile duct carcinoma, 16 y	No	URTI Chronic diarrhea	Died
24	2.5, 1986	c.409+3A>T	Gallbladder carcinoma, 28 y Rectal carcinoma, 29 y	No	URTI IPNA Neutropenia Chronic diarrhea Encephalitis Cryptococcus	Died
193	7, 1996	c.584 T>C	Metastatic neuroendocrine tumor (liver)	No	PNA Neutropenia Chronic diarrhea Oral ulcers Failure to thrive	Died
134	35.8, 1993	c.761 C>T	Cholangiocarcinoma, 46 y	No	URTI and LRTI PIP-PNA Chronic lung disease Chronic diarrhea + <i>Cryptosporidium</i> species + <i>Haemophilus</i> Sclerosing cholangitis	Died
185	3, 1971	Not reported	Neuroendocrine tumor Age not reported	No	URTI and LRTI PNA and Interstitial PNA Bronchiectasis Neutropenia (G-CSF) Chronic diarrhea + TPN Sclerosing cholangitis <i>Enterobacter</i> sepsis and <i>Staphylococcus</i> sepsis	Died
211	24, 1992	c.156+1G>T	Neuroendocrine carcinoma liver/biliary tract Age not reported	No	URTI and LRTI Neutropenia (G-CSF) Chronic diarrhea/esophagitis Sclerosing cholangitis	Died
192	0.5, 1996	c.584 T>C	High-grade epithelial dysplasia (pre-malignant) in the colon, s/p colectomy, 11 y	Yes Match sibling Bone marrow Nonablative + fludarabine + engraftment	URTI LRTI PIP-PNA RSV-induced pneumonitis Chronic diarrhea	Alive 16.5 y Karnofsky score 100%
167	0.75, 1978	c.590 C>A c.591-594 delCfs.V241X	AML 24 y	Yes MUD Bone marrow Daunorubicin (45/m ² d 1-3) Cytarabine (200 mg/m ² d 1-7)	URTI and LRTI PNA Neutropenia (G-CSF) Oral ulcers <i>Candida</i> esophagitis cGVHD	Alive 36 y Karnofsky score 90%

AML, Acute myeloid leukemia; *cGVHD*, chronic graft-versus-host disease; *G-CSF*, granulocyte colony-stimulating factor; *IPNA*, interstitial pneumonia; *LRTI*, lower respiratory tract infection; *MUD*, matched unrelated donor; *PIP*, *Pneumocystis jirovecii*; *PNA*, pneumonia; *RSV*, respiratory syncytial virus; *SP*, status post; *TPN*, total parenteral nutrition; *URTI*, upper respiratory tract infection.

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TABLE IV

Cause of death for patients with XHIGM not undergoing HCT (n = 22) and those undergoing HCT (n = 10)

ID	
Cause of death for patients not undergoing HCT (n = 22)	
24	Malignancy: Gallbladder and rectal carcinoma
134	Malignancy: Cholangiocarcinoma
185	Malignancy: Neuroendocrine tumor
193	Malignancy: Neuroendocrine tumor
206	Malignancy: Cholangiocarcinoma
211	Malignancy: Neuroendocrine tumor
25	Liver failure
142	Liver failure
38	Liver failure
210	Liver failure (sclerosing cholangitis)
6	Liver failure (sclerosing cholangitis; cirrhosis; chronic hepatitis B)
40	Liver failure (sclerosing cholangitis; cirrhosis)
116	Opportunistic infection (<i>Pneumocystis jirovecii</i>)
171	Opportunistic infection (<i>Candida glabrata</i> and <i>Pseudomonas aeruginosa</i>)
202	Opportunistic infection (<i>Pneumocystis jirovecii</i>)
143	Infection: Bilateral pneumonia (pathogen not known)
205	Infection: Bilateral pneumonia and hemophagocytosis (pathogen not known)
201	CNS: Stroke—hypertension
15	CNS: Progressive multifocal leukoencephalopathy
41	Unknown cause
78	Unknown cause
83	Unknown cause
Cause of death for patients undergoing HCT (n = 10)	
42	Adenovirus disseminated
123	Adenovirus disseminated
164	<i>Pneumocystis jirovecii</i>
65	<i>Cryptosporidium</i> (sclerosing cholangitis; <i>Salmonella</i> species)
105	GVHD
58	GVHD and VOD + hemorrhage after liver biopsy
63	VOD
43	Liver failure (<i>Cryptosporidium</i> , species, <i>Candida albicans</i> , <i>Staphylococcus aureus</i> , influenza-A, parainfluenza-2)
113	Liver failure: No infection specified
175	Progressive disease neurologic deterioration of unknown cause

CNS, Central nervous system; VOD, veno-occlusive disease.