JACI-D-16-00121R2

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

Short Title: Long term outcomes for X-linked hyper IgM syndrome

Key Words

X-linked hyper-IgM syndrome

CD40Ligand

Hematopoietic cell transplantation

Defects in class-switch recombination

Long term outcomes

Primary immunodeficiency

Lansky/Karnofsky scores

Abbreviations

XHIGM: X-linked hyper IgM syndrome

CD40LG: CD40Ligand

HCT : Hematopoietic cell transplantation; Hematopoietic stem cell transplantation.

rhG-CSF: Human-recombinant granulocyte –colony stimulating factor

REDCap: Research Electronic Data Capture

HR: Hazard ratio

CL: Confidence limits

GVHD: Graft versus host disease

VOD: Veno-oclusive disease

Capsule Summary: A survey of 176 patients with the XHIGM syndrome diagnosed between 1964 and 2013 finds similar overall survival whether treated with or without HCT, although recent experience may favor HCT, especially for those treated at a young age. Given the improvements in care, prospective study of contemporary cohorts is warranted.

ABSTRACT:

Background: X-linked hyper IgM syndrome (XHIGM) is a primary immunodeficiency with high morbidity and mortality compared to normal individuals. Hematopoietic cell transplant (HCT) has been considered a curative therapy, but the procedure has inherent complications, and may 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 in order 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 the Primary Immune Deficiency Treatment Consortium. Data was collected using a REDCap web application. Survival from time of diagnosis or transplant was estimated using the Kaplan-Meier method, compared using log-rank tests, and modeled using proportional hazards regression.

Results: Twenty-eight clinical sites provided data on 189 patients diagnosed with XHIGM between 1964 and 2013; 176 had valid follow-up and vital status information. Sixty-seven patients (38%) 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=0.671). However, risk associated with HCT decreased for diagnosis years 1987-1995; the hazard ratio was significantly < 1 for diagnosis years 1995-1999. Liver disease was a significant predictor of overall survival [HR (95% CL): 4.9 (2.2, 10.8), p<0.001]. Among survivors, those treated with HCT had higher median Lansky and Karnofsky scores than those treated without HCT (p<0.001). Among patients receiving HCT, 27 (40%) developed graft versus host disease, and most deaths occurred within 1 year of transplant.

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.

INTRODUCTION

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 “dysgammaglobulinemia” because patients had recurrent infections associated with low or absent levels of IgG and elevated levels of IgM. [2,3] The molecular defect is the result of mutations in the *CD40Ligand* (*CD40LG*) gene. [4] [5,6] [7] [8,9] [10-14] Binding of CD40L, expressed by activated CD4+ T-cells, to its receptor, CD40, constitutively expressed by B-cells, is critical for immunoglobulin isotype switching and an effective secondary antibody response. CD40L binding to CD40 expressed on dendritic cells and macrophages leads to their maturation, activation and cytokine secretion which contributes to an effective T cell response. This dual function explains the combined nature of the immunodeficiency. [15-20]

For the past two 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* is a presumed contributor to sclerosing cholangitis and hepatic/bile duct malignancies. In over 50% of cases, chronic or intermittent neutropenia is recognized; parvovirus induced red cell aplasia and progressive neurodegeneration of unknown etiology has also been reported. [21,22] The overall prognosis is poor with an average of 20% survival by age 25 years. [1,23-27]

Since the reported morbidity and mortality in XHIGM is high compared to normal individuals, HCT has been considered as 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 al compared long-term outcomes of 29 patients undergoing transplantation to 27 patients treated with conventional medical therapies and concluded that HCT improved the outcomes of patients with XHIGM. [42]

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* 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.

PATIENTS AND METHODS

This study is retrospective, observational and multinational. Physicians caring for patients with primary immunodeficiency diseases (PID) were identified through the Jeffrey Modell Foundation (JMF), United States Immunodeficiency Network (USIDNET), Latin American Society for Immunodeficiency (LASID), and the Primary Immune

Deficiency Treatment Consortium (PIDTC). The European Society for Immunodeficiency (ESID) published an announcement for this study in the ESID newsletter website. An email requesting participation in a survey was sent to 183 physicians. Survey data were collected under an approved Institutional Review Board (IRB) protocol titled “A Natural History Study of Long Term Outcomes of patients with X-Linked Hyper IgM syndrome” and managed using REDCap (Research Electronic Data Capture) hosted at UT Southwestern Medical Center Dallas. [43] A total of 106 fields were compiled and divided into four sections: (1) Demographics (Institution and Country of origin), age at diagnosis, year of diagnosis, family history of X-linked hyper IgM, 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 transplant, relationship of donor, source of stem cells, conditioning regimen, engraftment, evidence of graft vs host disease (GVHD); for those patients undergoing more than one HCT, the same questions were asked for each subsequent HCT; (4) Clinical presentation, post diagnosis treatment, and Lansky or Karnofsky scores at last follow up. For the complete survey instrument, see REDCap survey included in Repository Data.

Statistical Analyses

The study was designed for a target enrollment of 200 subjects and assumed an HCT prevalence of 40%. Sample sizes in the range 165-200 provide 80% power to detect an overall hazard ratio ≥ 1.8 between patients treated with or without HCT. Characteristics of patients at the time of diagnosis were summarized along with their ensuing medical management. Post-diagnosis survival was estimated using the Kaplan-

Meier (KM) method, and log-rank tests were used to compare survival. Proportional hazards regression of post-diagnosis 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 post-diagnosis survival were explored 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 *Pneumocystis jirovecii* Pneumonia, Mycobacteria, BCG infection, Parvovirus, Cytomegalovirus, or *Cryptosporidium*. Additionally, in the subgroup of HCT recipients, characteristics were summarized at the time of HCT, and log-rank tests were used to assess post-transplant 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. Time-line plots were created to show individual follow-up times from diagnosis for all patients and those in HCT subgroup. All analyses were programmed in SAS/STAT®, version 9.4 (SAS Institute Inc., Cary NC, USA).

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 out of 183 physicians contacted provided data. In order 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 subjects (7%) were excluded due to invalid follow-up time or vital status information, allowing analysis of 176 total patients.

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

Characteristics of the patients are summarized in Table 1. 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 - 59.3 years). Twenty-nine patients were diagnosed 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 illustrated in Table 2. Immunoglobulin replacement and *Pneumocystis jirovecii* prophylaxis was reported for 95% and 75% of patients, respectively. Forty-five percent of patients with neutropenia were treated with rhG-CSF, while azithromycin prophylaxis was used in only 8%. No statistical differences in these practices were observed based on country of origin except for transplantation practice ($p < 0.001$) (Figure 1 and Table 2): European patients (26/51; 51%) were more likely to have undergone HCT as compared to patients from North America (36/88; 41%) or those from South America (5/25; 20%), although 14/26 (54%) transplants performed on 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 post-diagnosis survival of XHIGM patients treated with or without HCT. The median survival time from diagnosis was 25 years for all patients (Figure 2A). No difference in overall survival was noted when patients were stratified by the year in which the diagnosis of XHIGM was made ($p=0.298$; Repository E Figure 1). 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=0.671, Figure 2B). The median survival time from diagnosis was similar between the two groups (25 years without HCT versus 20 years with HCT) (Figure 2B). These data were confirmed in the subgroup of patients with a known mutation in *CD40LG* (Repository Figure 2-3). No difference in survival was noted when birth was used as time 0 for the KM analysis (Repository Figure 4).

The study was powered to detect a hazard ratio ≥ 1.8 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 may have also changed over time. Figure 3 shows the hazard ratio for treatment with versus without HCT as a function of diagnosis 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 < 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: 57/67 (85%) of those treated with HCT and 87/109 (80%) of those treated without HCT. Those treated with HCT had higher median Lansky and Karnofsky age performance scores than those treated without HCT (100.0% with HCT versus 90.0% without HCT, p<0.001) (Figure 4)

Clinical factors associated with mortality

Affected organ system involvement at time of diagnosis is depicted in Repository Table 1 and 2. Documented infections were recognized in 80% of patients, in almost half of these (43%; 61/176), *Pneumocystis jirovecii* was the presenting manifestation

(data not shown), and it was common for patients to have had more than one organ affected. Thirty six (36/176; 20%) patients were found to have liver disease, which was in over 40% (16/36) of these cases, the presenting manifestation of XHIGM. While *Cryptosporidium* was not frequently identified amongst the whole cohort (13/176; 7%), it was noted in 25% (8/36) of those patients with associated liver disease. There was no trend in the identification of this pathogen over time, as it was observed in patients who had been diagnosed with XHIGM between 1987 to 2012. Three patients underwent liver transplantation, two also received a HCT; both of these patients are alive with Karnofsky score of 90%. The third patient was diagnosed with sclerosing cholangitis at age 33 years, XHIGM at age 36 years and underwent liver transplant 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 [HR (95% CL): 4.9 (2.2, 10.8), $p<0.001$] using best subset selection of clinical predictors at presentation in the proportional hazards model. The corresponding survival estimates are illustrated in Figure 5. In addition to liver/biliary involvement, the candidate pool of predictors at time of diagnosis included respiratory tract involvement, hematologic involvement, gastrointestinal disease, central nervous system involvement, failure to thrive, malignancy, and history of infection by *Pneumocystis jirovecii* pneumonia, Mycobacteria, BCG infection, Parvovirus, Cytomegalovirus, or *Cryptosporidium*.

A total of 8/176 (4.5%) patients developed a malignancy, which was associated with high mortality (6/8; 75%) (Table 3). Malignancy diagnosis ranged from before

XHIGM diagnosis (patient 206) to 25 years after diagnosis (patient 24). Only one patient had evidence of *Cryptosporidium.* All patients with tumors involving the bile ducts died.

Among decedents, the cause of death for non-HCT patients and transplanted patients is noted in Table 4. Malignancy as a cause of death was only noted for non-HCT patients. (Table 4).

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 to those patients treated without HCT (Table 1), no difference was noted between the two groups for year of diagnosis (without HCT: median 2001; range 1964-2013 versus HCT: median 2003; range 1978-2012; p=0.638); and total follow up time (without HCT: mean 8.7 ± 7.7 years versus HCT: mean 8.2 ± 6.4 years; p=0.866). Of 8 patients diagnosed at birth, 4 were transplanted.

Patients treated with HCT were less likely to have an established molecular diagnosis (60% with HCT versus 87% without HCT; p<0.001), were younger at time of diagnosis (Median age, 0.6 years with HCT versus Median age 1.6 years without HCT ; p<0.001), were less likely to have a family history of XHIGM (34% with HCT versus 50% without HCT;p=0.029) and were younger at last follow up (Median age, 8 years with HCT versus 13 years without HCT; p=0.001).

Transplant-related characteristics are outlined in Repository Table 3. Excluding subjects in whom conditioning data was not provided, 93% of myeloablated patients engrafted, and 85% of non-myeloablated patients engrafted (Fisher's exact p=0.384).

Forty percent (27/67) developed graft versus host disease (GVHD), most reported as acute (20/27 patients). Nine patients (13%) underwent a second HCT (7 of these had received myeloablative conditioning, and 2 were reported as non-myeloablated) and 1 received a total of 3 HCT transplants (data not shown).

While patients treated with HCT were diagnosed with XHIGM between 1978 and 2012, transplants were performed between 1996 to 2012. The median age at transplant was 2.9 years (range 0.1-24 years). The median time between diagnosis and transplant was 1.8 years (range 30 days – 23.25 years) and the mean follow up time post transplantation was 8.1 ± 6.4 years (range: 0.1 – 35.3 years). Post-transplant survival was estimated at > 80% at 10 years. Most deaths occurred within one year of transplant (Figure 6A). Given changes in transplantation practices, we evaluated if one-year survival has improved in the past two decades. We compared the first 10 years of transplantation practices to the following 8 years. That is, two transplant year intervals were defined: 1996-2005 and 2006-2013. The survival plot is shown in Repository E Figure 5. One-year survival is approximately 80% in the earlier transplant group and close to 90% in the later transplant group ($p = 0.057$). 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 diagnosed before 1993 ($p < 0.001$; Figure 6B). In contrast no difference in overall survival was found from time of diagnosis for all patients, including those with a known mutation in *CD40LG* and when stratified by whether they received a HCT or not. While not statistically significant, lower risk for HCT is noted in more contemporary cohorts, i.e. those patients with *CD40LG* mutation and diagnosed after 1993; n=112.(Repository Figure 6and 7)

Several transplant variables were explored as to whether they predicted survival: Age at transplantation predicted survival, reaching statistical significance at increased age (Figure 6C-F). Year of HCT, donor relationship, hematopoietic stem cell source, conditioning regimen, GVHD, or engraftment, did not influence survival (all log-rank $p>0.286$, Repository Figure 8 A-F) Liver disease at time of transplant was a predictor of poor outcome within the transplant group (Repository Figure 9).

For those patients undergoing transplantation, the cause of death is noted in Table 4. Infections and transplant related complications were the principalcause of death. HCT-related complications included veno-oclusive disease (VOD) and GVHD: Patient 58 received a non-myeloablative conditioning while patients 63 and 105 received myeloablative therapy. (Table 4)

Time line plots for post-diagnosis survival of XHIGM patients showing HCT intervals are noted in Repository Figure 10. Most patients undergoing HCT have short follow up time after transplantation with most under 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 XHIGM patients 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 (135) or without (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 has resulted in treatment recommendations which focus on the prevention of infections and the only proposed curative therapy is HCT.[27] While geographical differences were noted in HCT practices, no significant difference in geographical 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 *Pneumocystis jirovecii,* including 16% of patients in whom *Pneumocystis* was the presenting clinical manifestation, and less than 50% of patients with neutropenia were treated with rhG-CSF suggesting subtle differences in clinical care (Table 1-2).

One hundred and forty-four patients (81.8%) were alive at closure of enrollment ranging in age from 1 month to 60.7 years. The oldest survivor was 60.7 years, had not been transplanted and was oldest amongst all patients at last follow up. The mortality rate of 2.2%/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

to 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 (Figure 2A). This is similar to the findings of a recent 14-year (1998-2012) retrospective analysis of 56 Japanese patients with XHIGM, in which the 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 XHIGM patients treated with or without HCT. We chose to perform post-diagnosis survival estimates as provided by 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 1) but in other groups of PID where 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 (Figure 2B). 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 deaths. The analysis represented in Figure 2A and Figure 2B conveys the message that cumulative survival decreases steadily with time from diagnosis. Of note, as few patients are followed beyond 10 years, when deaths do occur after this time, they have a greater effect on the estimated survival probability due to the the decreased numbers remaining at risk

Expanding on this idea, a timeline plot was created which demonstrates follow-up times from diagnosis for each patient (Repository Figure 10) Amongst the HCT

subgroup, 5 deaths occurred 10 years after diagnosis, 4 of these less than a year after transplant. The length of follow up is certainly a limitation of the study. It is possible that if the length of follow up were longer, i.e. into the fourth, fifth and sixth decade of life, the KM curves may diverge in favor of transplant.

Furthermore, recognizing that transplant practices have improved in the past four decades (better HLA typing methods, better antifungal and viral monitoring), we sought to evaluate if this observation could have influenced survival. Indeed, a survival benefit for the transplant group was gradually noted after 1987, reaching statistical significance (hazard ratio of <1) in the late 1990s, when sample size, follow up time and power were adequate for analysis (Figure 3). While not statistically different, one-year survival after transplantation appears to have improved after 2006 as compared to the previous decade (Repository E Figure 5).Lastly, survivors treated with HCT experienced slightly better well-being as measured by Lansky and Karnofsky scales than those without HCT ($p<0.001$, Figure 4).

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 to those not transplanted 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 previously reported series (Repository Table 1). [1,23,27] While almost 50% of patients had a family history of XHIGM, only 10% of these boys were diagnosed at birth (Table1). This is lower than previously reported.[1,44] In this series, *Pneumocystis jirovecii* was the presenting manifestation in 43% of patients, which is remarkably similar to data reported almost two decades ago. [1,27] In contrast, only 26% of patients from the Latin America Registry present with *Pneumocystis* infection.[25] Depending on pathogen exposure, other infections may dominate at time of presentation as demonstrated by a recent Chinese cohort, where 30% of patients came to medical attention with complications following BCG vaccination.[46] *Cryptosporidium* is well recognized as a significant cause of morbidity and mortality in patients with XHIGM. In this series, only 13/176 (7.4%) patients had this organism identified, less than initially reported from the European and North American studies . [1,27] However, *Cryptosporidium* was identified in the majority of patients who had liver disease at presentation (13/16; 81%). This relatively low percentage overall may reflect the difficulty of identifying the organism in stool. Newer PCR-based diagnostic methodologies for detection of *Cryptosporidium* provides an opportunity for prospective studies to better judge the impact of this organism on survival of 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 time of transplantation (Figure 5 and Repository Figure 9). The clinical data on pulmonary status was not collected at time of transplant, therefore we cannot comment

396 on whether pre-existing lung disease at time of transplantation influenced survival, as
397 has been previously reported. [38,47] An important difference in mortality between
398 transplanted and non-transplanted patients is the development of malignancy. This was
399 only noted in the non-transplanted group and the time to such complication was
400 reported as late as 25 years after diagnosis.

401 For the subgroup of patients who were transplanted, eighty-five percent of
402 patients were surviving. The overall survival is similar to that reported in the Japanese
403 experience comprising patients from 1998 to 2012 [42] and improved as compared to
404 68% overall survival from the European experience with HCT for XHIGM between 1993
405 and 2002. [41] Transplant survival was influenced by year of diagnosis and age at
406 transplantation (Figure 6 B-F). Those patients diagnosed before 1993 fared worse,
407 suggesting improvement in the care of XHIGM patients after the genetic basis for the
408 disease was discovered. Older age at transplantation has been recognized as a risk
409 factor for poor outcome when PID patients are transplanted. [48-50] Similarly, in patients
410 with XHIGM, survival worsened as the age at transplantation increased past five years
411 (Figure 6 E-F). Taken together if the decision for HCT is agreed upon, this should be
412 done before liver disease and preferably before age 10 years (Figure 5 -6).
413 Nonetheless, with improvement in the care of patients with XHIGM prior to
414 transplantation betterment in transplantation outcomes could also be seen for older
415 XIGM patients as observed in other PID, as long as organ damage and infections are
416 controlled. [51,52]

417 Taken together, the data presented suggest an improvement in HCT survival for
418 XHIGM patients diagnosed 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% developed GVHD, underscoring the need for detailed analysis of transplant outcomes and how they impact a patient's quality of life.

Many questions remain, for example, 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 may impact long term survival. Does transplantation prevent the appearance of malignancy, an important cause of death for non-transplanted patients? How are transplant related morbidities, including graft failure and GVHD impacting patient's quality of life? Finally, will gene therapy and evolving recombinant technologies be better options in the future?[53]

When caring for patients with life-limiting diseases, improving survival while optimizing quality of life are the primary goals. For patients with XHIGM the long term survival remains guarded. For those patients who have potential HCT donors, transplantation performed before the age of 10 years and prior to the development of liver diseases may offer not only a survival advantage but improved long term general wellbeing. 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 four 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.

ACKNOWLEDGEMENTS

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

This work was supported by a grant from Jeffrey Modell Foundation to MdlM.

The Primary Immune Deficiency Treatment Consortium (PIDTC) is supported by NIH Office of Rare Diseases, National Center for Advancing Translational Sciences and National Institute of Allergy and Infectious Disease U54 AI 082973 and R13AI094943.

AUTHOR CONTRIBUTIONS

(1) the conception and design of the study
(2) Acquisition of data,
(3) Analysis and interpretation of data,
(4) Drafting the article
(5) Revising it critically for important intellectual content,
(6) Final approval of the version to be submitted

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FIGURE AND TABLE LEGENDS

FIGURES:

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

Figure 2. Kaplan-Meier estimate of post-diagnosis survival of 176 patients with XHIGM for all patients (A) and by HCT group (B). Whereas median survival time was 25 years for all patients, there was no statistical difference in survival probability between the HCT and non-HCT treatment groups (p=0.671)..

Figure 3. Estimated hazard ratio and 95% confidence band for treatment with HCT versus without HCT in N=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

Figure 4. Lansky/Karnofsky scores (%) of surviving XHIGM patients

Figure 5. Kaplan-Meier estimates of post-diagnosis survival of XHIGM patients by liver disease. Among all patients with XHIGM, liver disease at time of diagnosis is a significant negative predictor of survival (p<0.001)

Figure 6. A. Kaplan-Meier estimate of post-transplant survival of 67 XHIGM patients treated with HCT. B. Kaplan-Meier estimates of post-transplant survival by year of diagnosis : Before 1993 (1964-1992) and after 1993 (1993-2013). C. Kaplan-Meier estimates of post transplant survival by age at transplantation: <1 year vs >1 year; D. <2 years vs >2 years; E. <5 years vs >5 years; F. <10 years vs >10 years

TABLES:

Table 1. Characteristics of study patients (N=176). * Fisher's exact tests were used for categorical variables and Wilcoxon rank-sum for continuous and ordinal variables. [§] 8 patients were diagnosed at birth (4 received no HCT and 4 underwent HCT)

Table 2. Characteristics of clinical practice. [¥] Fisher's exact tests for geographical differences in clinical management; *No response = 4; **No response = 7;[§] Eighty three

556 percent (51) of patients who had *Pneumocystis jirovecii* pneumonia were subsequently
557 placed on prophylaxis.

558 Table 3. Clinical Characteristics of XHIGM patients with malignancy. * yrs= years; **
559 AML= Acute myeloid leukemia.

560 Table 4. Cause of death for non-HCT patients (n=22) and for HCT patients (n= 10);
561 **GVHD=Graft versus Host Disease; ** VOD=Veno-occlusive disease.*

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REPOSITORY INFORMATION

Repository information includes REDCap Survey, 8 figures and 3 tables

Repository Figures and Tables Legends

Repository E Figure 1. Kaplan-Meier estimates of post diagnosis survival of XHIGM patients stratified by year of diagnosis in intervals of approximately 10 year categories. Four diagnosis year categories were defined: between 1964 and 1984, 1985-1994; 1995-2004 and 2005-2013. The first two decades were combined due to the small number of patients (only 12 patients altogether) as compared to the subsequent years,indicated in the numbers at risk. Pairwise comparison analysis of the 4 diagnosis year intervals show no significant differences (p=0.298). The most significant difference is between 1985-1994 (green dashed) and 2005-2013 (blue dashed), p = 0.080. Five patients with missing year of diagnosis were excluded.

Repository E Figure 2. Kaplan-Meier estimates of post diagnosis survival of XHIGM patients with known mutation in *CD40LG* (N= 135) and by HCT.

Repository E Figure 3. Kaplan-Meier estimates of post diagnosis survival of XHIGM patients by evidence of *CD40LG* mutation.

Repository E Figure 4. Kaplan-Meier estimates of survival from birth of XHIGM patients by HCT.

Repository E Figure 5. Kaplan-Meir estimates of post transplantation survival stratified by year of transplant. Two transplant year intervals were defined: 1996-2005 and 2006-2013. 1 patient with missing year of transplant was excluded.

Repository E Figure6. Kaplan-Meier estimates of post diagnosis survival of XHIGM patients stratified by year of diagnosis: Before 1993 (1964-1992) and in 1993 or after (1993-2013). A. Represents patients within the whole cohort; N= 172 (4 subjects did not have year of diagnosis reported); B. Represents patients with known CD40LG mutations, N=131 (4 subjects did not have year of diagnosis reported); C. Twenty-nine patients diagnosed with XHIGM before 1993 stratified by whether they received a HCT; D. One hundred and forty three patients with XHIGM diagnosed in 1993 or after and stratified by whether they received a HCT.

Repository E Figure 7. Patients with known mutation in *CD40LG*. Kaplan-Meier estimates of post diagnosis survival of XHIGM patients by HCT and year of diagnosis: A. N=19 patients diagnosed before 1993 (1964-1992); and B. N=112 patients diagnosed in 1993 and after (1993-2013).

Repository E Figure 8. Kaplan-Meier estimates of post-transplant survival of HCT patients by A.Year of transplant: 1996 to 2004 vs 2005 to 2013; B. Relation of donor: Related vs unrelated; C. Stem cell source: UCB (umbilical cord blood) vs bone marrow vs PBSC (peripheral blood stem cells); D. Conditioning regimen: MA = myeloablative vs Non-MA= non-myeloablative; E. Development of GVHD (graft vs host disease): None vs presence and F. Reported engraftment vs no evidence of engraftment.

Repository E Figure 9.Kaplan-Meier estimates of post-transplant survival of XHIGM patients treated with HCT by liver disease at time of transplant.

Repository E Figure10. Timeline plot of post-diagnosis survival for each patient. Each timeline is black up to the time of the transplant and red afterward. Timelines capped with arrows indicate patients still living, capped timelines indicate patients have died. A. All patients (N=176) showing HCT intervals. B. Subgroup of patients who received HCT (N=67).

Repository E Table 1. Affected Organ/System involvement at diagnosis for patients with XHIGM (N=176). Patients may have been described as having more than one organ/system involved.

Repository E Table 2. Central nervous system disorders at presentation (N= 20/176). *Patients may have been described as having more than one manifestation.

Repository E Table 3. Transplant specific characteristics for 67 patients with XHIGM.*Four patients did not have GVHD status reported.

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