Hematopoietic stem cell transplantation as treatment for patients with DOCK8 deficiency

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Keywords

DOCK8 deficiency, HSCT, combined immunodeficiency

Abbreviations

ADV	adenovirus
BUMAC	myeloablative busulfan
BURIC	reduced dose busulfan
CID	combined immunodeficiency
CMV	cytomegalovirus
DOCK8	dedicator of cytokinesis 8
EBV	Epstein-Barr virus
GVHD	Graft versus Host disease
HHV6	human herpesvirus 6
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
HSV	herpes simplex virus
MSD	matched sibling donor
MFD	matched family donor
MUD	matched unrelated donor
MMFD	mismatched family donor
PBSC	peripheral blood stem cells
PFT	pulmonary function test
RIC	reduced intensity regimen
TBI	total body irradiation
TREO	treosulfan based regimen
UCB	umbilical cord blood

Abstract:

Background: Biallelic variations in the DOCK8 gene cause a combined immunodeficiency with eczema, recurrent bacterial and viral infections, and malignancy. Natural disease outcome is dismal, but allogeneic hematopoietic stem cell transplantation (HSCT) can cure the disease.

Objective: To determine outcome of HSCT for DOCK8 deficiency and define possible outcome variables.

Methods: We performed a retrospective study of the results of HSCT in a large international cohort of DOCK8 deficient patients.

Results: We identified 81 patients from 22 centers transplanted at a median age of 9.7 years (range: 0.7-27.2) between 1995 and 2015. After median follow-up of 26 months (3-135), 68 of 81 patients are alive (84%). Severe acute (III-IV) or chronic graft versus host disease (GVHD) occurred in 11% and 10% respectively. Causes of death wereinfections (n=5), GVHD (5), multi-organ failure (2) and pre-existent lymphoma (1). Survival after matched related (n=40) or unrelated (35) HSCT was 89% and 81%, respectively. Reduced toxicity conditioning based on either treosulfan or reduced-dose busulfan resulted in superior survival compared to fully myeloablative busulfan-based regimens (97% vs. 78%; p=0.049). 96% of patients aged <8 years at HSCT survived, compared to 78% of those ≥8 years (p=0.06). Of 73 patients with chimerism data available, 65 (89%) had >90% donor T-cell chimerism at last follow-up. Not all disease manifestations responded equally well to HSCT: eczema, infections and Mollusca resolved better than food allergies or failure to thrive.

Conclusion: HSCT is curative in most DOCK8 deficient patients, confirming this approach as the treatment of choice. HSCT using a reduced toxicity regimen may offer the best chance for survival.

Highlights box:

1. What is already known about this topic?

Biallelic variations in the *DOCK8* gene cause a combined immunodeficiency with dismal natural disease outcome, which can be treated by allogeneic HSCT.

2. What does this article add to our knowledge?

HSCT with a reduced toxicity conditioning results in excellent survival and disease correction, regardless of donor type.

3. How does this study impact current management guidelines?

The encouraging results of this analysis may be helpful for patient counselling and guiding clinical decision making in future DOCK8 deficient patients.

Introduction

Biallelic mutations or deletions in the gene encoding the dedicator of cytokinesis 8 (*DOCK8)* cause a combined T- and B- lymphocyte immunodeficiency (1, 2), characterized by severe and recurrent skin and systemic infections, severe allergic disease, and predisposition to malignancy (3, 4), and which had initially been described as the autosomal recessive variant of Hyper-IgE syndrome (5). After discovery of the causative gene in 2009, two larger cohorts have been published, both demonstrating the severity of this disease and its dismal outcome (3, 6, 7). Only about a third of patients reach age 30 without HSCT and about 75% develop severe, life-threatening disease complications before age 20 (6).

Soon after, two case reports of patients, who had undergone HSCT long before genetic diagnosis was possible, demonstrated the possibility of cure with HSCT (8, 9). Several case reports and small case series on the outcome of HSCT with various donor types have since been published (10-17). Most of them report encouraging results, possibly skewed by publication bias. While these reports have been helpful in directing many patients with DOCK8 deficiency to earlier HSCT, it still remains unclear which conditioning regimens or donor types will yield the best outcomes. Furthermore, some of the case reports hinted at the fact that not all disease manifestations, notably food allergies, may be equally well corrected by HSCT (8, 11, 18). To address these questions, larger and more comprehensive HSCT cohorts need to be studied.

Based on a multi-institutional retrospective chart-based review conducted on behalf of the inborn errors working party of the European Group for Blood and Marrow Transplantation (EBMT) and the European Society for Primary Immunodeficiencies (ESID) this manuscript reports on the largest cohort of DOCK8 deficient patients treated by HSCT so far.

Methods

Data accrual and statistics

A case report form asking for pseudonymized chart-based data of transplanted patients was sent to authors of our previous paper on the DOCK8 phenotype (6) and to members of the inborn errors working party of the EBMT and ESID and was posted on the ESID website. The data collection concluded on 31.12.2016. This retrospective chart review received a waiver of approval by the ethics committee of the Ludwig-Maximilians-University of Munich, Germany. German patients or their respective caregivers gave their written informed consent for inclusion in the German pediatric stem cell transplantation registry (PRST) which was approved by the ethics committee of the Medizinische Hochschule Hannover. International centers had to receive approval for data transfer from their respective ethics committee or a waiver if applicable. Kaplan Meier survival estimates and cumulative incidence rates were compared using the log rank test (Prism 5, GraphPad, La Jolla, CA, USA). Other analyses utilized the chi-square or Fisher exact test and were accepted as significantly different at a level of $p<0.05$.

Patients

Included in this study were patients with a confirmed bi-allelic variation affecting the *DOCK8* gene who underwent a first HSCT between 1.1.1995 and 31.12.2015. Partial information on 36 patients in this study was previously reported in the paper by Aydin et al (6).

Definitions

Unrelated donors were considered matched (MUD) if they were at least 9/10 or 10/10 HLA allele matched. Due to the different dosing regimens for i.v. and oral busulfan, all busulfan dosages were converted to a dose equivalent to oral dosing in order to make them comparable. Conditioning regimens containing busulfan were considered to be myeloablative if the total dose was equivalent to an oral dose of ≥14mg/kg or was targeted to an AUC of ≥70.000ngxml/h and reduced intensity when the total dose was <14mg/kg or targeted to an AUC of <70.000ngxml/h.

GVHD was graded according to modified Glucksberg criteria for acute, and according to NIH consensus criteria for chronic GVHD (19, 20). Severe infections were defined as sepsis, meningitis, or pneumonia requiring hospitalization and supplemental oxygen or mechanical ventilation.

The method for determining resolution of symptoms post HSCT was left at the local physician's discretion.

Results

Patient and transplant details

Data from 81 patients (43 female, 38 male) receiving a first HSCT from 22 centers in 11 countries were included. The median age at HSCT was 9.7 years (0.7 - 27.2). Donors were matched sibling donors (MSD) in 34 transplants, other matched family donors (MFD) in 6, mismatched family donors (MMFD) in 6, matched unrelated donors (MUD) in 33 and unrelated cord blood (UCB) in 2. Bone marrow was the preferred stem cell source, used in 63 patients, peripheral blood stem cells (PBSC) in 16, and cord blood in 2. Conditioning was based on myeloablative busulfan (BUMAC) in 31 patients, while in 17 reduced doses of busulfan (BURIC) were used. A treosulfan-based regimen (TREO) was applied in 17 patients. In vitro T-cell depletion was applied in one MUD recipient and in four of the six MMFD recipients, while the two other MMFD had post-transplant cyclophosphamide. The median follow-up after HSCT was 26 months (3-135). More detailed patient and transplant information is given in table 1.

Survival

The entire cohort of 81 patients had a 2-year overall survival (OS) probability of 84 % (95% confidence interval 73%-91%; figure 1A) and potential outcome variables were tested.

There was no significant survival advantage after HSCT from a MSD or MFD compared to a MUD with 2-year OS probabilities of 89% (73-96) and 86% (66-95), respectively. Recipients of a MMFD had a 2-year OS probability of 66% (20-90), which was also not statistically different to the other groups (p=0.18; figure 1B). The conditioning regimen did have an impact on HSCT outcome. Two-year OS probabilities after TREO, BURIC, BUMAC, or any other reduced intensity regimen (RIC) were 100%, 94% (63-99), 78% (57-90) and 79% (47-93; p=0.25; figure 1C), respectively. Using either a TREO or BURIC regimen resulted in a significantly better OS at 97% (80-100) versus using BUMAC, which yielded an OS of 78% (57-90; p=0.049; figure 1D). The median age in this cohort was 9.7 years (range 0.7-27.2). It was therefore prudent to test the influence of age at HSCT on survival. However, no age cut-off resulted in a significant result. There was a trend towards better survival in patients receiving their HSCT below the age of 8 years versus above with 2-year OS of 96% (74-99) and 78% (63-88; p=0.06), respectively (figure 1E). Lastly, the date of HSCT had a significant influence on survival. Patients transplanted from 2011 to 2015 had a 2-year OS of 92% (81-96) as compared to 57% (28-78) for those who had their HSCT from 1995 to 2010 (p=0.01; figure 1F). Of the 13 deaths post HSCT, the most common cause of death was infection (n=5 patients; bacterial sepsis n=3, unknown=2), as well as infection associated with GVHD (n=5; bacterial sepsis n=2, fungal, n=1, viral n=2). Multi organ failure was reported as cause of death in 2 cases; 1 patient succumbed to a T-cell lymphoma, pre-existent before HSCT, which was not EBV-driven. Virus reactivation/infection in the immediate post-transplant period occurred in 31 patients and two of the

deaths were associated with viral disease (CMV and adenovirus). The frequency of virus infection/reactivation was statistically not different between surviving and deceased patients (p=0.547) (table 3).

In summary, HSCT performed from a MSD/MFD or MUD after TREO or BURIC conditioning after 2010 resulted in superior outcomes in this cohort.

GVHD

Acute GVHD was reported in 27 of 81 patients resulting in a cumulative incidence of 33%. Of these 22 (27%) had a severity of grade II-IV and 9 (11%) of grade III-IV. Of the 73 patients alive at more than 100 days post HSCT 7 developed chronic GVHD (10%), 3 mild, 2 moderate and 2 severe by NIH consensus criteria. In 5 of the 13 deaths GVHD was a contributing factor.

Engraftment and chimerism

Of the 73 patients with chimerism data available at last follow up, 64/73 (88%) had a global donor chimerism of 90% or higher, 1/73 (1%) between 80% and 90%, 4/73 (5%) between 20% and 80% donor and 4/73 (5%) between 0% and 20% (figure 2A). Two of the 81 patients did not engraft, both died during or after second HSCT. One had received a T-cell depleted MMFD graft after BUMAC and one an UCB after non-myeloablative conditioning. The T-cell donor chimerism was 90% or higher in 65/73 patients (89%), between 80% and 90% in 4/73 (5%), between 20% and 80% in 3/73 (4%) and between 0% and 20% in 1/73 (1%) at last follow up (figure 2B). Twenty-nine of the 31 patients (94%) receiving a BUMAC regimen had a global donor chimerism of 90% donor or higher, one had a chimerism of 40% and one rejected. Of the 28 patients with a TREO or BURIC regimen and with chimerism data available, donor chimerism was 90% or higher in 25 (89%) and between 20% and 80% in 3 (11%).

Thus, engraftment in this cohort was solid and there was no discernable effect of the intensity of the conditioning regimen on the degree of donor chimerism.

Symptom resolution post HSCT

In early single patient reports inconsistent resolution of DOCK8 deficiency related symptoms after successful HSCT was described. Thus, we asked for changes in disease related symptoms at last follow-up (median 26 months [3-135]).

Eczema, mollusca and recurrent upper airway infections responded very well to HSCT. Eczema was reported as resolved or improved in 70/71 patients (99%) who suffered from it before HSCT and mollusca in 34/36 (94%) (figure 3A and B). Upper airway infections were described as less frequent than before HSCT or occurring at a normal frequency for age in 66/71 affected patients (93%) (figure 3C). Food allergies and impaired pulmonary function tests (PFT) responded less to HSCT. Food allergies resolved or improved in 34/56 (61%) patients, and since 13/56 (23%) had not been exposed

to their specific allergens after HSCT, resolution or improvement was observed in 34 of those 43 patients who had exposure to their respective allergens post HSCT (79%) (figure 3D). Impaired PFT improved or normalized in 26/47 (55%) patients, stabilized in 12/47 (26%) and worsened in 2/47 (4%) (figure 3E). Of 47 patients who had failure-to-thrive, another frequent symptom of DOCK8 deficiency, 30 (64%) normalized or were catching up, 8 (17%) were unchanged, 2 (4%) too old to catch up (no improvement post-puberty) and in 5 (11%) it was too early after HSCT to tell (figure 3F). Of 12 patients with malignancies before HSCT, 11 remained in remission at last follow-up. One patient with lymphoma progressed and died. Another patient who had total body irradiation (4Gy) as part of her conditioning developed secondary thyroid cancer 7 years after HSCT, was successfully treated and remains in remission 7 years later. Finally, the treating physicians were asked whether they thought their patients had benefitted from HSCT and 76/81 replied. The answer was “yes, definitely” for 65/76 patients (85%), “somewhat improved” for 2/76 (3%), “too early to tell for 3/76 (4%) and “patient died” for 6/76 (8%).

In summary the vast majority of surviving patients had improvement or resolution of their disease related symptoms.

Discussion

DOCK8 deficiency, which was initially described as autosomal recessive Hyper IgE syndrome, is a combined immunodeficiency (CID) with a high mortality rate (1, 2, 5). Single case reports of patients transplanted years before the causative gene had been identified showed that HSCT was curative (8, 9). Two larger and partially overlapping cohorts later confirmed a poor natural disease outcome with patient survival of about 50% at age 20 in the absence of HSCT, as well as high rates of malignancy, life threatening infections or CNS events (6, 7). We present the data relating to HSCT outcomes in the largest cohort of DOCK8 deficient patients to date, and found that outcomes are generally good when HSCT was performed with a reduced toxicity regimen. All disease manifestations are potentially cured by HSCT.

In general, patients with CID are thought to have a survival advantage if transplanted as children (21). This may be in part due to the development of PID related comorbidities that occur over time, and the desire to have an earlier intervention to prevent more significant disease complications. As the prior study by Aydin et al demonstrated, the majority of patients with DOCK8 deficiency will develop a life-threatening infection, CNS event or malignancy by age 20 (6). In this study with a median age at HSCT of almost 10 years we were not able to identify an ideal age range for HSCT in DOCK8 deficiency. A much larger study will be needed to make such a recommendation. It is still possible that HSCT has a favorable risk/benefit ratio in adolescents or young adults with DOCK8 deficiency. Out of 16 patients with an age at HSCT of 16 years or higher in our cohort, 14 survived, which is in line with recent reports on good HSCT outcomes in adolescents and young adults with primary immunodeficiencies (22, 23). In a disease like DOCK8 deficiency which is characterized by severe systemic and cutaneous viral infections, it is expected that pre-existing viral disease in the host will result in more infectious complications during and after HSCT. In this cohort this was not the case. Only two of the 13 HSCT-associated deaths were in part attributed to viral disease and only 33% of patients experienced viral reactivation/infection. This means that while special attention should still be placed on prevention of virus infections after HSCT, the presence of pre-existing viral disease should not be an exclusion criterion for transplant. The reported incidence of severe acute and chronic GVHD in this cohort is low, given the high load of viral disease in DOCK8 deficiency. This may be caused by the fact that about half of the donors were MSD or MFD. This study showed no impact on OS with 9/10 or 10/10 MUD compared to MSD/MFD. Our data may suggest that outcome after haploidentical HSCT in DOCK8 deficiency is inferior. However, two deaths in this very small group (n=6) occurred in the 1990-ies and all four patients transplanted with modern in-vitro or in-vivo T-cell depletion strategies (TCRαβ/CD19-depletion or post-transplant cyclophosphamide, n=2 each) survived. This encouraging outcome after MMFD HSCT in DOCK8 deficiency is in line with recent case reports (13, 16, 17).

This large multi-center patient series allows the analysis of the impact of different HSCT strategies on outcome. Although a wide variety of conditioning regimens were reported ranging from fully myeloablative to an unconditioned stem cell infusion in one patient (24), it was possible to compare fully myeloablative busulfan-based regimens to reduced toxicity regimens based on either busulfan or treosulfan, demonstrating a significant survival benefit for these reduced regimens. The fact that 89% of patients achieved >90% donor chimerism with these regimens indicates that regimens based on reduced doses of busulfan with or without pharmacokinetic monitoring or treosulfan - as they are currently recommended by the inborn errors working party of EBMT and ESID - may preferentially be used for patients with DOCK8 deficiency (25). It remains to be explored in the future whether patients with specific pre-HSCT comorbidities would require conditioning regimens with the degree of myeloablation and immunosuppression tailored to their specific needs.

This study comprehensively analyses the correction of all disease related manifestations in DOCK8 deficiency by HSCT. As expected from previous smaller case series, eczema and mollusca resolved or improved in almost all affected patients. The fact that food allergies only slowly regress after successful HSCT could be confirmed here, which may be explained by the long-lived nature of host-derived, IgE-producing plasma cells (18). Impaired pulmonary function tests before HSCT did not improve or normalize in 30% of the patients within the relatively short follow-up period. This argues strongly for a strategy of transplanting patients before permanent lung damage has developed, as this may not only negatively impact their quality of life but also long-term survivorship. Most of the pre-existing malignancies remained in remission after HSCT and only one patient developed thyroid cancer after HSCT, which may also have been caused by the irradiation containing conditioning. This suggests that the strong predisposition towards malignancy in DOCK8 deficiency is corrected or at least improved by HSCT, although long-term follow-up is still limited. This may be especially true for the malignancies of B-cell origin. Whether this also remains true for the cancers of epithelial origin, which are more frequent in DOCK8 deficiency than in other CID (6), remains to be evaluated in larger cohorts with a longer follow-up. The hope is that with good immune reconstitution and better control of HPV infection, the incidence of HPV related squamous cell carcinomas will decrease. In our previously published cohort of 136 DOCK8 deficient patients, 12.5% of patients were reported to have autoimmunity (6). In this current cohort none of the patients were reported to have had autoimmunity as a post HSCT complication or as a cause of death. Due to this relative infrequency, we did not investigate resolution of autoimmunity after HSCT.

While this is the largest cohort of transplanted DOCK8 patients published to date, there are limitations to this study. Its retrospective and multicenter design may implicate a bias in selecting conditioning regimens for individual patients based on their clinical conditions. The relatively small numbers of patients, incomplete chimerism data and lack of immunological parameters post HSCT did not allow us to analyze the impact of lineage specific chimerism and immunological reconstitution on clinical outcome and symptom resolution. Ideally these should be studied in a prospective manner. An

increasing number of reports of vascular abnormalities including vasculitis have been reported in DOCK8 deficiency, which was not systematically assessed in this cohort. The outcome and long-term prognosis of patients with these complications should be addressed in future studies. It may also be possible that individuals with biallelic DOCK8 variations and an extremely mild clinical phenotype who don't require HSCT may be discovered, even if no current publication suggests this.

In summary this study confirms that patients with DOCK8 deficiency can expect excellent survival and disease correction if transplanted with modern HSCT strategies. We believe that the overall encouraging results of this analysis will be helpful for patient counselling and guiding clinical decision making in future DOCK8 deficient patients.

Author contributions:

SEA and MHA designed the study and wrote the manuscript. SEA, MHA and RA acquired, analyzed and interpreted the data. All authors except RA provided patient data. All authors critically revised the manuscript and approved the final version of the manuscript.

Tables

Table 1:

n=	81
female/male	43/38
median age at HSCT (years)	9.7 (0.7-27.2)
donor type	
MSD	34
MFD	6
MUD	32
MMUD	1
HLA match 10/10	20
9/10	10
8/10	1
8/8	1
6/6	1
MMFD	6
UCB	2
stem cell source	
bone marrow	63
PBSC	16
cord blood	2
conditioning	
busulfan based	48
myeloablative	31
BU/CY	12
BU/FLU	19
reduced*	17
treosulfan based (all TREO/FLU)	17
other reduced intensity	14
with TBI (200-400cGy)	4
other myeloablative	1
none	1
serotherapy used	38

Table 1: Patient and transplant characteristics. BU/CY: busulfan cyclophosphamide; BU/FLU: busulfan fludarabine; TREO/FLU: treosulfan fludarabine; MFD: matched family donor; MMFD: mismatched family donor; MSD: matched sibling donor; MUD: matched unrelated donor; MMUD: mismatched unrelated donor; PBSC: peripheral blood stem cells; TBI: total body irradiation; UCB: unrelated cord blood.
*: busulfan i.v. dose equivalent to <14mg/kg p.o. or busulfan targeted to an AUC of <70.000ngxml/h

385 **Table 2:**

acute GVHD	27/81	(33%)
I	5	(6%)
II	13	(16%)
III	6	(7%)
IV	3	(4%)
II-IV	22	(27%)
III-IV	9	(11%)
chronic GVHD (f/u>100d)	7/73	(10%)
mild	3	(4%)
moderate	2	(3%)
severe	2	(3%)

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387 **Table 2: GVHD.** Incidences of acute and chronic GVHD.

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Table 3:

		time point	
	number of patients with virus infection/reactivation	early (< day 100)	late (> day 100)
surviving (68/81)	25/68 (37%)	CMV 15 EBV 4 HSV 3 ADV 4 HHV6 1 BK 2 other 1	EBV 2 HSV 1 VZV 2
deceased (13/81)	6/13 (42%)	CMV 3 EBV 2 HSV 1 HHV6 1	CMV 1 (persistent) EBV 1 (persistent) ADV 1

Table 3: Viral infections/reactivations in surviving and deceased patients. Frequency of virus infections/reactivations in surviving and deceased patients. A single patient may have had multiple viruses. The frequency of virus infection/reactivation was statistically not different between surviving and deceased patients (p=0.547). ADV: adenovirus; BK: human polyoma virus 1; CMV: cytomegalovirus; EBV: Epstein-Barr virus; f/u: follow-up; HHV6: human herpesvirus 6; HSV: herpes simplex virus; VZV: varicella zoster virus.

Figure legends

Figure 1. Overall survival (OS). Kaplan-Meier analysis of overall survival post HSCT of the entire cohort (A), by donor type (B), by type of conditioning (C,D), by age at HSCT (E) and by the year of HSCT (F). BUMAC: busulfan-based myeloablative conditioning; BURIC: busulfan-based reduced intensity conditioning; RIC: reduced intensity conditioning; TREO: treosulfan-based conditioning.

Figure 2: Chimerism at last follow-up. Donor chimerism at last follow-up in n=73 patients in whom data were available in whole blood (A) and in T-cells (B).

Figure 3: Correction of disease related symptoms by HSCT. Treating physicians were asked how they rated the correction of symptoms associated with DOCK8 deficiency after HSCT. PFT: pulmonary function tests.

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