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Stem cell transplantation for congenital dyserythropoietic anemia. An analysis from the European society for blood and marrow transplantation

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Running heads:

Stem Cell Transplantation for CDA

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Congenital Dyserythropoietic Anemias (CDAs) are a group of heterogeneous disorders characterized by hyporegenerative anemia and ineffective erythropoiesis, with relative reticulocytopenia, and iron overload¹. Specific morphological aspects of late erythroblasts in the bone marrow form the most important, albeit non-specific, feature of the disease. Morphology has always been the most important tool for diagnosis and is still used to classify the disease into three classical forms and variants.² Nonetheless, in the last few years, mutations of six specific genes related to the regulation of DNA and cell division were identified as causative.³⁻⁵

Patients with CDA usually show anemia, jaundice, splenomegaly, ineffective erythropoiesis and the typical marrow features. Somatic abnormalities involving fingers and nails can be part of the clinical features.

The management of the disease is generally limited to blood transfusion and iron chelation. Interferon- α treatment has also been successfully used in patients with CDA type I,^{6,7} whereas splenectomy proved to reduce the number of transfusions in CDA II.⁸

Overall, the prognosis of CDA patients is good;² however, stem cell transplantation (SCT) represents the only curative option for this disease. Some reports have shown its efficacy; however, data from the literature are scarce and limited to a very small number of patients, mostly transplanted from sibling donors.⁹⁻¹⁶

In this retrospective study we describe the outcome of SCT in a large cohort of patients with CDA. The study was conducted on behalf of the Severe Aplastic Anemia Working Party (SAAWP) of the EBMT and relied on data from patients affected with CDA who underwent SCT and were registered in the EBMT Database. Clinical information on the disease was collected by a questionnaire distributed to participating centers and the details on transplant procedures were obtained by analyzing the database.

Engraftment was defined as neutrophil count $>0.5 \times 10^9/L$ for at least 3 consecutive days. Primary graft failure was defined as neutrophil count never reaching $>0.5 \times 10^9/L$ and secondary graft failure was defined as a decrease in neutrophil count to a lower level after initial engraftment. Overall survival (OS) and event free survival (EFS), defined as survival without rejection, graft loss or a second transplant, were calculated using the Kaplan-Meier product limit estimation method; differences in subgroups were assessed by the Log-Rank test. Median follow-up was estimated using the reverse Kaplan-Meier method. Cumulative incidences of grade II-IV acute graft versus host disease (aGvHD), of limited/extensive chronic GvHD (cGvHD) and of graft failure were analyzed separately in a competing risks framework, and subgroup differences were assessed by Gray's test. Competing events for graft failure, acute/chronic GvHD, include 2nd transplant, relapse and death. All estimates were reported with a corresponding 95% confidence interval, and p-values <0.05 were considered significant. Iron overload was defined as ferritin serum level >1000 mg/dl or as the presence of pathological liver iron concentration by MRI.

Between 1996 and 2016, 39 patients (22 males), with a median age of 5.1 years (range 0.9-38.2) underwent SCT following a conditioning regimen that was myeloablative in all but one cases. SCT was performed because of transfusion dependency alone (34) or associated with iron overload (5). Patients' clinical characteristics are shown in Table 1. Only one patient in this cohort has been previously reported.¹⁰

All patients were engrafted. The 3-year incidence of secondary graft failure was 12% (1-23%). Median days to neutrophil and platelet recovery were 21 (range 10-75)

and 34 (range 16-399), respectively. Conditioning regimens and transplant features are shown in Table 1. Median follow-up was 44 months (range 13-71, with 13 transplants performed in the last two years of the study period). OS and EFS at 36 months were 71% (55–87%) and 45% (45–63%), respectively (Fig 1 A, B). Ten patients died due to GvHD (6), infection (3) or multi-organ failure (1). Patients who were transplanted from unrelated donor (UD) had an inferior outcome compared with those engrafted from matched sibling donors [OS 51% (26-76%) vs 92% (76-100%) $p=0.05$]. OS of patients with iron overload was significantly worse [45% (18–72%) vs. 90% (76-100%), $p=0.007$] compared with the ones transplanted without (Fig 1 C, D). Survival was no different between patients transplanted before and after 2010 and in patients conditioned with or without fludarabine. The incidence of graft failure in patients transplanted with and without iron overload was 17% (0–38%) and 6% (0–17%), respectively ($p=0.382$). Graft failure was 6% (0–17%) and 16% (0–32%) in patients transplanted from MSD and UD, respectively ($p=0.497$). Of note, this probability, due to competitive causes, was significantly higher in patients transplanted with vs. without iron overload (59% vs. 17%, $p=0.024$) and from a UD vs. a MSD, respectively (55% vs. 31%, $p=0.05$) (Fig 1 E and F). A trend towards a higher incidence of grade II-IV aGvHD was also seen in patients transplanted from a UD (59% vs. 25%, $p=0.06$) and with iron overload (53% vs. 25%, $p=0.1$), as compared to those engrafted from matched sibling donors and with no iron overload, respectively. Severe (Grade III-IV) aGvHD incidence was 29%, and was significantly higher ($p=0.005$) in UD (53%) over MSD transplants (10%).

To the best of our knowledge, this is the largest reported cohort of patients transplanted for CDA. Anecdotal experiences have been previously published, including a total of thirteen children, composed of CDA type I,⁹ type II,¹⁰⁻¹³ and type III,¹⁶ transplanted from sibling donors in all cases except for 3 patients who were transplanted from a UD.^{11,12,16} Of particular note, our study, which included 44% of patients transplanted from a UD, showed that donor type still affects the outcome since MSD SCTs have superior OS and engraftment.

Another factor affecting the outcome of our cohort was iron overload, which is an intrinsic feature of patients with CDA due to hepcidin down-regulation and ineffective erythropoiesis. We also found an association between iron overload and GvHD that might become fully significant if a larger number of patients was available. Previous reports on thalassemia^{17,18} showed that tissue damage secondary to iron accumulation may enhance the risk of transplant-related toxicity and predispose patients to a higher incidence of aGvHD. This outlines the importance of a pre-transplant definition of the risk the patients may incur, which generated a dramatic improvement of the outcome in the case of thalassemia patients (Pesaro risk classes).¹⁷ The lack of such a pre-SCT selection in CDA patients might explain their worse outcome compared with other transfusion-dependent, hemolytic anemias like thalassemias. Indeed, the better outcome of CDA patients transplanted without iron overload seems to support this hypothesis. Amongst the risk factors, iron overload in CDA candidates for SCT needs to be carefully evaluated and definitely reduced with effective chelation.

Graft rejection of this CDA cohort was comparable to that seen in thalassemia patients¹⁹ and was negatively affected by donor type (UD was worse) and iron overload. This points to the need for careful evaluation of the choice of donor type in the decision making process.

Most patients were conditioned with myeloablative regimens including Busulfan/Treosulfan. In the limited number of cases included in this study, no difference was noted compared to patients who, in addition, received Fludarabine or

Cyclophosphamide. Of note, the only patients of our cohort who received a non-myeloablative conditioning regimen had a successful outcome, as did the only previously reported CDA subject,¹⁶ who was conditioned with Fludarabine-Cyclophosphamide and 1-day course TBI. This raises the issue of the appropriateness of reduced-intensity conditioning in CDA. Unfortunately, we could not address this aspect in this study due to lack of available data, but it might be worth investigating in future analyses.

In conclusion, despite the lower overall outcome compared to previous reports on thalassemia patients, SCT may represent an alternative therapeutic option in CDA with outcomes appearing to be superior in patients transplanted from MSD and without iron overload. Indeed, iron overload is an important factor that needs to be controlled and eventually treated before transplant. In this respect, CDA patients might benefit from pre-SCT risk assessment, e.g. like Pesaro criteria, which may favorably impact on the overall outcome. The high incidence of graft failure and aGvHD and the lower overall survival observed in patients transplanted from UD should be carefully considered and discussed with parents, if a familial donor is not available.

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PATIENTS' CHARACTERISTICS	N 39	SCT from sibling	SCT from MUD	36 months OS
CDA sub-types				
type I	10 (26%)	8	2	80%
type II	13 (33%)	5	8	61%
type IV	1 (3%)	0	1	
xlda (gata-1)	1 (3%)	0	1	
missing	14 (35%)			
Molecular mutation				
SEC23B	6 (15%)	2	4	
GATA-1	2 (5%)	1	1	
CDAN1	1 (3%)	1	0	
No mutation	24 (62%)	14	10	
Missing	6 (15%)	4	2	
Somatic abnormalities	8/39 (20%)			
Skeletal	4	2	2	
Skin	1	0	1	
Neurological	3	1	2	
Retina	0	0	0	
Dysmorphic face	1	1	0	
Macrocephaly	1	1	0	
Pre-transplant treatment	20 (51%)			
Splenectomy	2 (5%)	0	2	
Chelation treatment	13 (33%)	7	6	
IFN	5 (13%)	1	4	
Clinical manifestation at SCT				
Hepatomegaly	15 (38%)	9	6	77%
Jaundice	9 (23%)	6	3	41%
Splenomegaly	18 (46%)	12	6	68%
Iron overload	17 (43%)	8	9	51%
Age at HSCT, years (median, range)	5.1 (0.9 – 38)	4(1-38)	7(0.9-31)	
Time from diagnosis to SCT, months (median, range)	34.8 (2.4 - 377)	23(2-177)	55(2-377)	
Performance status at HSCT (Lansky or Karnofsky)				
<90	5 (13%)	3	2	
90-100	28 (71%)	16	12	
missing	6 (15%)			
Year of SCT:				
Before 2010	18 (46%)	11	7	65%
After 2010	21 (54%)	11	10	79%
Donor type:				
Identical sibling	20 (51%)			90%
Unrelated donor	17 (44%)			45%
Other relative	2 (5%)			
HLA Match				
10/10	12	4 (29%)	7 (47%)	66%
<10/10	19	10 (71%)	8	58%
Missing	8			
Stem cells source:				
Bone Marrow	30 (76%)	18	12	
Peripheral Blood	7 (18%)	3	4	
Cord Blood	2 (5%)	1	1	
Busulfan-based conditioning	28 (72%)	18	10	
Bu-Cy	10	10	0	
Bu-Cy-ATG	9	6	3	
Bu-Flu-ATG	3	2	1	
Bu-Flu-TT	1	0	1	
Bu-Flu-TT	1	0	1	
Bu-Flu-Cy-ATG	2	0	2	
Bu-Flu-LPAM -ATG	1	0	1	
Bu-Cy-LPAM-ATG	1	0	1	
Treosulfan-based conditioning	8 (20%)	1	7	
Treo-Flu-TT	2	0	2	
Treo-Flu-TT-ATG	4	0	4	
Treo-Flu-LPAM-ATG	1	1	0	
Treo-Cy -ATG	1	0	1	
Other conditioning	3 (8%)			
Cy	1	2	0	
Cy-ATG	1	1	0	
Missing	1			

Secondary graft failure	8	4	4
Acute GvHD, grade III-IV (100 days)	11	2	9
Chronic GvHD (36 months) Limited/Extensive	7	5	2
Death	10	2	8
Follow-up, median months (range)	44 (13 – 71)		

Table 1. Patients' characteristics and transplants' features. *Bu*, Busulfan. *Flu*, Fludarabine. *TT*, Thiotepa. *Cy*, Cyclophosphamide. *L-PAM*, Melphalan. *GvHD*, Graft-versus-Host Disease. *OS*, Overall Survival

Fig. 1. Outcome of patients with CDA undergoing SCT. (A) Overall Survival. (B) Event Free Survival. (C) Overall survival according to donor type. (D) Overall survival according to iron overload. (E) Graft failure incidence according to donor type. (F) Graft failure incidence according to iron overload.

