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Case Report

# The role of allogeneic stem cell transplantation in severe erythropoietic protoporphyria in adults and young adults: timing and modalities

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## Introduction

Porphyrias are caused by enzymatic dysfunctions in the haem biosynthesis metabolic pathway.[1]

Erythropoietic protoporphyria (EPP), the most common porphyria in children, that occurs in about 1 in 74,300 individuals, is an autosomal disorder, characterized by acute, severe, non-blistering phototoxicity within minutes of exposure by sunlight, and caused by pathogenic variants in the ferrochelatase (*FECH*) gene.[2,3] The reduced enzyme activity results in the accumulation, during erythropoiesis, of protoporphyrin IX (PPIX), which activated by sunlight exposure, generates singlet oxygen and radical reactions, leading to tissue damage and excruciating pain.

PPIX is excreted solely through the hepatobiliary route, and in case of accumulation can aggregate in hepatocytes and precipitate in bile canaliculi, causing severe hepatotoxicity, that may require liver transplantation (LT).[4-6] However persistence of PPIX accumulation in the bone marrow causes the recurrence of liver disease in most patients, justifying sequential hematopoietic stem cell transplantation (HSCT) and LT to cure EPP-related hepatopathy.[7,8]

Congenital erythropoietic porphyria (CEP) is a rare autosomal recessive disorder caused by a deficiency in uroporphyrinogen III synthase (UROS), leading to the accumulation of type I porphyrins during erythropoiesis. The prognosis is poor

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in severely affected patients due to the destruction of subcutaneous tissues and pancytopenia. Death often occurs early in adulthood.[9,10] Since the 1990s, HSCTs have been the therapeutic choice for severe pediatric cases (Table 1).

Here, we present four patients with either EPP or CEP who underwent HSCT after the age of fifteen.

## Clinical cases

Patient #1 was a 17-year-old EPP-patient who underwent a LT from his father in 2001, in the context of EPP-related hepatopathy. After five months, the patient underwent HSCT from the same haploidentical donor. The conditioning regimen was based on fludarabine and total body irradiation (TBI 2cGY). HSCT was complicated by primary graft failure. He continued transfusions and ferrochelating therapy to prevent hemochromatosis. He died 11 years later.

Patient #2, a 32-year-old man diagnosed with EPP at the age of three, underwent a first LT in 2009 for liver cirrhosis. In the following years, he presented a progressive worsening of liver function and a liver biopsy in 2013 confirmed the recurrence of the initial disease (micro-nodular cirrhosis, with a very strong fibrotic component and pigment overload typical of PPIX deposition).

He therefore underwent a second LT, followed by a HSCT, to prevent EPP recurrence on the graft. The patient underwent a non-myeloablative matched-unrelated transplant after conditioning with fludarabine, busulfan and thymoglobulin. He demonstrated excellent neutrophil engraftment on day +19. Peripheral blood donor chimerism was 100% by day +30. He did not have any signs of GvHD or infectious complications. His blood counts were normal. Free erythrocyte PPIX levels were normal and he did not experience any photosensitivity. Nine years after HSCT, he is alive but he underwent a third LT for arterial stenosis and severe infectious complications on second liver transplant.

Patient #3 was a woman diagnosed with EPP at the age of five, which only presented regular mild episodes of photosensitivity. At the age of 40, she experienced a first severe cholestatic hepatitis episode and was treated with ursodeoxycholic acid for six months. The cholestasis resolved and PPIX levels dropped to pre-hepatitis levels.

Eight months later, a second severe episode of cholestatic hepatitis occurred (bilirubin up to 500 $\mu$mol/L), requiring prolonged hospitalization in an intensive care unit. Hydroxycarbamide, red blood transfusions and plasma exchanges contributed to suppress endogenous hematopoiesis and the production of porphyrins, allowing full recovery. Liver biopsy showed a parenchyma of respected architecture, with portal fibrosis and discrete steatosis, and pigment overload typical of PPIX deposition.

She was referred for an allogeneic HSCT from a 10/10 HLA-matched unrelated donor. Conditioning regimen, preceded by desensitization protocol by plasma exchanges, intravenous immunoglobulin and rituximab (donor specific antibody higher than 12,000 mean fluorescence intensity (MFI) by single antigen bead assay), consisted of fludarabine, busulfan and thymoglobulin.

Neutrophil engraftment occurred on day +24 and peripheral blood donor chimerism was 94.2% by day +30 and 96% by day +100. There were no GvHD or infectious complications. Free erythrocyte protoporphyrin and the plasma-free protoporphyrin were repeated and dropped to normal levels at day 28 after HSCT (Figure 1). She had complete resolution of photosensitivity and she largely returned to a normal life. With 22 months of follow up, the patient is fine, with only mild persistent thrombocytopenia.

Patient #4 was diagnosed with CEP at the age of two, mostly with skin involvement. At four years old, he underwent a first matched-unrelated allogeneic HSCT after a myeloablative conditioning regimen. Post-transplantation, his blood count was normal, he did not show any signs of GvHD or infectious complications and he showed a marked improvement in skin lesions. However, after 10 years, he presented with moderate cytopenia, new erosive, bullous skin lesions with scleroderma areas and functional joint impotence. Erythrocyte porphyrins increased to a very high level (24 $\mu$mol/L) in red blood cells (n <1.9). Peripheral blood chimerism was 76% recipient.

At the age of 22, he underwent a second HSCT from a matched-unrelated donor after a reduce intensity conditioning regimen. He achieved neutrophil engraftment on day +18 and a full donor chimerism. No acute GvHD occurred. Two years after HSCT, the patient leads a normal life, with normal protoporphyrin levels.

## Discussion and conclusions

EPP and CEP have great clinical variability related to heterogenous residual enzymatic activities; while numerous therapies have been applied, HSCT is the only curative treatment for severe forms of the diseases. From 1991, when the first HSCT was performed for CEP, there have been about thirty reports of, mainly pediatric, patients (Table 1).

The four cases we present may expand the already known experience about HSCT in porphyrias, to young adults and adults. Two patients presented the resolution of disease manifestations achieving normal protoporphyrin levels, one had primary graft failure (conditioning regimen was retrospectively not sufficient for engraftment) and the last experienced late secondary graft failure but was rescued by thae second transplant. None experienced acute nor chronic GvHD.

HSCT is certainly feasible, from any stem cell source or any type of donor, when the disease is severe. In the past, a myeloablative conditioning regimen was preferred, however engraftment seems to not be lower with non-myeloablative conditioning and minimization of toxicity is a priority in patients with liver failure and non-malignant disease. Hepatic involvement requires careful pre-transplant evaluation, including liver biopsy.

From a metabolic point of view, the efficacy of HSCT depends on the initial level of toxic porphyrin production and on the level of myeloid chimerism reached, i.e., the higher the initial porphyrin production, the lower the level of residual native erythropoietic cells must be for the patient to be asymptomatic. In patient #4, a 76% recipient chimerism was associated with sufficient erythrocyte porphyrins production

**Table 1 – Individuals with EPP (erythropoietic protoporphyria) and CEP (congenital erythropoietic porphyria) treated using stem cell transplantation. Patients transplanted after 15 years old are presented in bold.**

| UPN EPP patient | Ref.◆ | Genotype | Age[1] (years or months) | Sex (F/M) | Country | Liver Transplant before HSCT[2] (yes/no) | No. of liver transplant | Conditioning regimen (HSCT) | RIC/MAC | GvHD prophylaxis | Donor | PPE before/ after HSCT | Alive/Dead | Cause of death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| #1 | —- | c.899delTG heterozygous in exon 8 + hypomorphic allele IVS3-48 C/T; p.V300VfsX22 exon8 | 17 yrs | M | France | Yes, | 1 | Flu- TBI• | RIC | Tacro-MMF | Haplo | Primary graft failure | Dead 11 yrs post-HSCT | Progression EPP |
| #2 | —- | c.490 C>T p.R164W + c.645G>C p.R215P | 23 yrs | M | France | yes | 3 | Flu-Bu-Thymo• | RIC | CsA-MTX | MUD 9/10 | 389.6 μmol/L 0.8μmol/L | Alive 9 yrs post-HSCT RD | —- |
| #3 | —- | Complete deletion of FECH + IVS3-48C | 43 yrs | F | France | no | —- | Flu-Bu-Thymo• | RIC | CsA- MMF | MUD 10/10 | 295.1 μmol/L 1.9 μmol/L | Alive 22 months post-HSCT RD | —- |
| *5[3] | Poh-Fitzpatrick MB, 2002 | Missense mutation C185>G (Pro62>Arg) | 47 yrs | F | USA | no | —- | Bu-Cy-Etoposide | N/A | CsA-PDN | Sibling | N/A | Alive 5 yrs post-HSCT RD | —- |
| *6 | McGuire BM, 2005 | N/A | N/A | M | USA | yes | 2 | N/A | N/A | N/A | N/A | N/A | Dead 3 mo post-HSCT | Sepsis |
| *7 | Rand EB, 2006 | Heterozygous low expression IVS3-48C | 12 yrs 14 yrs | M | USA | yes | 1 | TBI-Cy Bu-Flu-Cy-Thymo | MAC | N/A N/A | Sibling Sibling | N/A | Alive 1 year post-HSCT | —- |
| *8 | Wahlin S, 2007 | IVS3-48C “null allele” mut. (930G>A) | 62 yrs N/A | M | USA | no | —- | Flu-Cy-Thymo Flu-Cy-TBI-Thymo | RIC RIC | Tacro-Siro CsA-MTX | MUD 10/10 MUD 10/10 | N/A | Alive 30 mo post-HSCT | —- |
| *9 | Smiers FJ, 2010 | Missense mut. FECH | 9 yrs | M | Holland | yes | 1 | Flu-Treo-Cy-Thymo-Melphalan- Alemtuzumab[4] | RIC | MMF-PDN | Haplo | N/A | Dead 8 mo post-HSCT | CMV infection |
| *10 | Wahlin S, 2010 | N/A | 57 yrs | M | England | yes | 1 | N/A | N/A | N/A | N/A | N/A | Dead | Infectious complications |
| *11 | Cheung CY, 2015 | Heterozygous low expression IVS3-48C | 21 yrs | M | Hong Kong | no | —- | Flu-Cy-TBI-Thymo | RIC | N/A | MUD 10/10 | N/A | Alive 5 months post HSCT | —- |
| *12 | Windon AL, 2017 | [315-348 T>C] | 26 yrs | M | USA | yes | 1 | Flu-Bu-TBI | RIC | Tacro-MTX | MUD10/10 | N/A | Alive 8 months post HSCT | —- |

| UPN CEP patient | Ref.◆ | Genotype | Age[1] (years or months) | Sex (F/M) | Country | Liver Transplant[2] (yes/no) | N° of liver transplant | Conditioning regimen (HSCT) | RIC/MAC | GvHD prophylaxis | Donor | Porphyrins before/ after HSCT | Alive/Dead | Cause of death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| #4 | —- | c.205G>A; p.A69T homozygous | 4 yrs 22 yrs | M | France | no | —- | Bu-Cy-Thymo• Flu-Bu-Thymo• | MAC RIC | CsA-MTX CsA | MUD 10/10 MUD 10/10 | 816 nmol/L 6 nmol/L | Alive 2 yrs post-HSCT RD | —- |
| *13 | Besnard C, 2020 | [c.217T>C, p.(Cys73Arg)] [c.560A>C, p.(Gln187Pro)] | 13 mo 21 mo | F | France | no | —- | Bu-Cy Bu-Cy | MAC MAC | CsA-MTX CsA-MTX | Sibling Sibling | N/A | Alive 24 yrs post-HSCT | —- |
| *14 | Besnard C, 2020 | [c.217T>C, p.(Cys73Arg)] [c.217T>C, p.(Cys73Arg)] | 26 mo 28 mo | F | France | no | —- | Bu-Cy Bu-Cy-Thymo | MAC MAC | CsA CsA | Haplo Haplo | N/A | Alive 22 yrs post-HSCT | —- |
| *15 | Besnard C, 2020 | [c.205G>A, p.(Ala69Thr)] [c.217T>C, p.(Cys73Arg)] | 13 mo | F | France | no | —- | Bu-Cy-Thymo | MAC | CsA | MUD 10/10 | N/A | Alive 3 yrs post-HSCT | —- |
| *16 | Besnard C, 2020 | [c.10C>T, p.(Leu04Phe)] [c.673G>A, p.(Gly225Ser)] | 4 mo | M | France | no | —- | Bu-Cy-Thymo | MAC | CsA | MUD10/10 | N/A | Dead | Acute liver failure |
| *17 | Besnard C, 2020 | [c.217T>C, p.(Cys73Arg)] [c.634T>C, p.(Ser212Pro)] | 7 mo 40 mo | F | France | no | —- | Flu-Bu-Thymo Flu-Bu-Thymo | MAC MAC | CsA- MMF CsA- MMF | MUD 10/10 MUD 10/10 | N/A | Alive 3 yrs post-HSCT | —- |
| *18 | Besnard C, 2020 | [c.205G>A, p.(Ala69Thr)] [c.244G>T, p.(Val82Phe)] | 8 mo | M | France | no | —- | Flu-Bu-Thymo | MAC | CsA- MMF | MUD 10/10 | N/A | Dead | Hepatic aGvHD; TAM |
| *19 | Kauffman L, 1991 | N/A | 11 yrs | F | England | no | —- | Bu-Cy | MAC | CsA | Sibling | N/A | Dead eight months post-HSCT | CMV infection |
| *20 | ThomasC, 1996 | N/A | 22 mo 30 mo | F | France | no | —- | Bu-Cy Bu-Cy | MAC MAC | CsA-MTX CsA-MTX | Sibling | N/A | Alive 1 year post-HSCT RD | —- |
| *21 | Zix-Kieffer I, 1996 | N/A | 4 yrs | F | France | N/A | N/A | N/A | N/A | N/A | Sibling | N/A | Alive 10 months post-HSCT RD | —- |
| *22 | Tezcan I, 1998 | URO synthase missense mutation G188R | 4.5 yrs | F | Turkey | no | —- | Bu-Cy | MAC | CsA | Sibling | N/A | Alive 35 months post-HSCT RD | —- |
| *23 | Shaw PH,2001 | N/A | 2 yrs | F | USA | no | —- | Bu-Cy | MAC | CsA | Sibling | N/A | Alive 15 months post-HSCT RD | —- |
| *24 | Harada FA,2001 | C73R | 2 yrs | F | USA | no | —- | N/A | N/A | N/A | MUD10/10 | N/A | Alive 16 months post-HSCT RD | —- |
| *25 | Dupuis-Girod S, 2005 | Homozygous missense mutation A69T | 4 yrs | M | France | no | —- | Bu-Cy-Thymo | MAC | CsA-MTX | MUD10/10 | N/A | Alive 3 yrs post- HSCT RD | —- |
| *26 | Dupuis-Girod S, 2005 | Homozygous missense mutation A69T | 4 yrs | F | France | no | —- | Bu-Cy-Thymo | MAC | CsA-MTX | MUD10/10 | N/A | Alive 2 yrs post-HSCT RD | —- |
| *27 | Phillips JD, 2007 | GATA 1 R219W | 3 yrs | M | USA | no | — | N/A | N/A | N/A | MUD10/10 | N/A | Alive 2 yrs post-HSCT RD | —- |
| *28 | Taibjee SM, 2007 | N/A | 7 yrs | F | England | no | —- | Flu-Bu-Cy | MAC | CsA | Sibling | N/A | Alive 3 yrs post- HSCT RD but cGvHD | —- |

**Table 1 (*continued*)**

| UPN CEP patient | Ref.◆ | Genotype | Age[1] (years or months) | Sex (F/M) | Country | Liver Transplant[2] (yes/no) | N° of liver transplant | Conditioning regimen (HSCT) | RIC/MAC | GvHD prophylaxis | Donor | Porphyrins before/ after HSCT | Alive/Dead | Cause of death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *29 | Faraci M,2008 | Homozygous URO synthase 217T/ C Cys73Arg | 12 yrs | M | Italy | no | —- | Bu-Thiotepa-Cy- Thymo | MAC | CsA-MTX | MUD10/10 | N/A | Alive 7 yrs post-HSCT RD | —- |
| *30 | Lebreuilly-Sohyer I, 2010 | p.Cys73Arg p.Ala69Thr | 18 mo | M | France | no | —- | N/A | N/A | N/A | MUD 10/10 | N/A | Alive 2 yrs post-HSCT RD | —- |
| *31 | Singh S, 2012 | UROS gene (not spec) | 14 yrs | M | India | no | —- | Flu-Cy- Thymo | RIC | CsA-MTX | Sibling | N/A | Alive 4 yrs post-HSCT RD | —- |
| *32 | Martinez Peinado C, 2013 | C73R/C73R (UROS gene) | 7 mo | M | Spain | no | —- | Bu-Cy-Thymo | MAC | CsA-MTX | MUD 10/10 | N/A | Alive 1 yrs post-HSCT RD | —- |
| *33 | Karakurt N, 2015 | UROS gene GATA-1 | 5 yrs | M | Turkey | no | —- | Bu-Cy | MAC | CsA | Sibling | N/A | Alive 3 yrs post-HSCT RD | —- |

UPN: unique patient number; Ref.: reference CsA: cyclosporin; F: female; M: male; MMF: mycophenolate mofetil; Tacro: tacrolimus; MTX: methotrexate; PDN: prednisone; N/A: not available; Flu: fludarabine; Bu: busulfan; Thymo: thymoglobulin; Cy: cyclophosphamide; TBI: Total body irradiation; MUD: matched-unrelated donor; Siro: sirolimus; Haplo: haplo-identical; RD = resolution of disease manifestations; aGvHD: acute graft-versus-host disease; cGvHD: chronic graft-versus-host disease; TAM: transplant associated microangiopathy; RIC: reduced intensity conditioning, MAC: myeloablative conditioning; yrs: years; mo: months

# Our patients are in green

* patients from literature; 1: age at HSCT; 2: liver transplant was performed before HSCT; • Conditioning regimen doses of our patients: Flu-TBI: fludarabine (30 mg/m2/day on days -5, -4, -3) and TBI 2 Gy; Bu-Flu- Thymo: fludarabine (30 mg/m2/day on days -5, -4, -3, -2 and -1), busulfan (3.2 mg/kg on days -4 and -3) and thymoglobulin (5 mg/kg on days -2 and -1)

3: Patient #5 underwent HSCT for AML; 4: Patient *9, because of anaphylactic shock after thymo, received melphalan and alemtuzumab in addition.


◆ Ref: Poh-Fitzpatrick MB, Wang X, Anderson KE et al. Erythropoietic protoporphyria: altered phenotype after bone marrow transplantation for myelogenous leukemia in a patient heteroallelic for ferrochelatase gene mutations. J Am Acad Dermatol. 2002; 46: 861–866.

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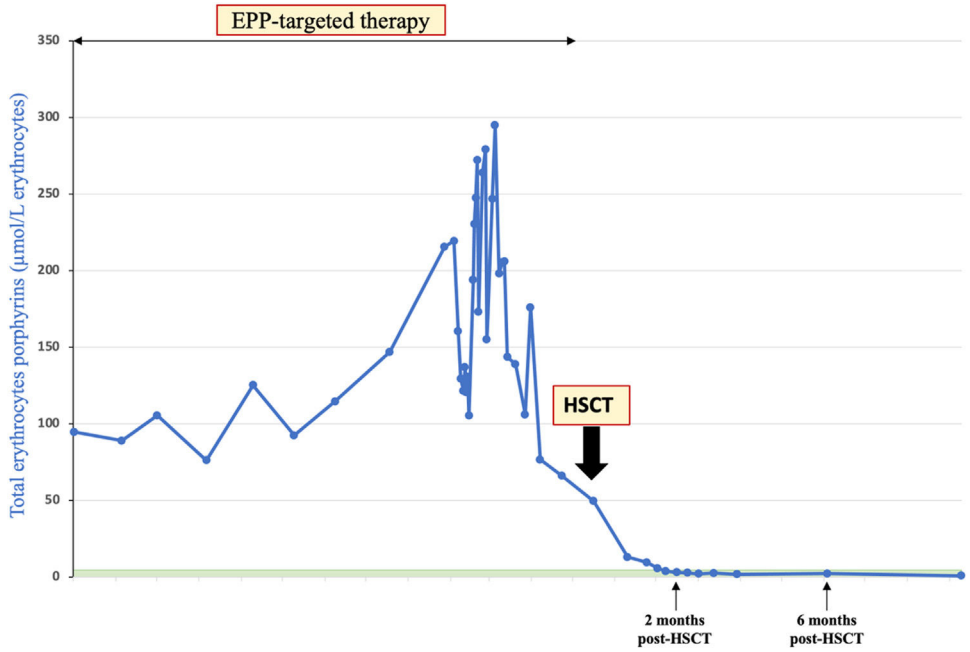


**Figure 1 – Evolution of patient #3 total erythrocytes porphyrins level. Green area indicates the normal range. HSCT: hematopoietic stem cell transplantation.**

(3.529 nmol/mmol creatinine) to induce severe symptomatology. It is therefore important to target full myeloid chimerism and normal erythrocyte porphyrins, especially in CEP patients.

In conclusion, HSCT should be evaluated for high-risk adults and young adult patients, with EPP and liver involvement. If possible HSCT must be perform before LT to prevent long-term complications inherent to solid organ transplantation; after LT it is necessary to prevent the inevitable relapse of the disease.

## Conflicts of interest

The authors declare no competing financial interests.

## Author contribution

C.F and F.S. generated the idea, collected the data and edited the manuscript; A.P. gave his contribution as experts in the porphyria's field. M.B., participated in patient treatment and follow-up at regional study sites. All authors read and approved the final manuscript.

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