Received: 9 January 2023 | Revised: 5 March 2023 | Accepted: 13 March 2023

DOI: 10.1002/pbc.30334

Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

RESEARCH ARTICLE

Hematopoietic stem cell transplantation with reduced toxicity conditioning regimen in mitochondrial neurogastrointestinal encephalopathy syndrome

Gülcihan Ozek[1] | Serap Aksoylar[1] | Sema Kalkan Uçar[2] | Ebru Canda[2] | Mediha Akcan[1] | Ozgür Cartı[1] | Zuhal Onder Siviş[1] | Yeşim Oymak[1] | Havva Yazıcı[2] | Bridget Bax[3] | Fatma Derya Bulut[4] | Merve Yoldaş Çelik[2] | Fehime Erdem[2] | Mahmut Çoker[2] | Savaş Kansoy[1]

[1]Department of Pediatrics, Division of Pediatric Hemathology and Oncology, Ege University Medical Faculty, Izmir, Turkey

[2]Department of Pediatrics, Division of Metabolism and Nutrition, Ege University Medical Faculty, Izmir, Turkey

[3]Department of Cell Biology, Institute of Molecular and Clinical Sciences, St George's University of London, London, UK

[4]Department of Pediatrics, Division of Metabolism and Nutrition, Çukurova University Medical Faculty, Adana, Turkey

Correspondence
Gülcihan Ozek, Department of Pediatrics, Division of Pediatric, Hemathology and Oncology, Ege University Medical Faculty, Bornova, Izmir, Turkey.
Email: gulcihanozek@yahoo.com, gulcihan.ozek@ege.edu.tr

Abstract

Background: Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disorder due to mutations in the *TYMP* gene. Clinical findings are characterized by neurologic manifestations and severe gastrointestinal dysfunction. The syndrome is usually fatal, the most effective treatment appears to be hematopoietic stem cell transplantation (HSCT).

Procedure: In this retrospective study, we evaluated HSCT that was performed using a reduced toxicity myeloablative conditioning regimen in patients with MNGIE at our center.

Results: A total of six allogeneic transplant procedures were performed in four patients. Three patients had fully matched donors, and one patient had a haploidentical donor. Treosulfan-based myeloablative conditioning regimen was applied in five of six transplants. Bone marrow was used as a stem cell source. One patient is being followed up in the 4th year of posttransplant with full chimeric and without graft versus host disease (GVHD). One patient died of acute stage IV gastrointestinal system GVHD. Two patients underwent second transplantation due to engraftment failure, one of which was the patient who had a haploidentical transplant.

Conclusions: Treosulfan-based regimen is well tolerated, although engraftment failure with this conditioning regimen can be a significant problem. We share our haploidentical transplant experience, which will be the first reported case in the literature.

KEYWORDS
hematopoietic stem cell transplantation, MNGIE, treosulfan

Abbreviations: AHSCT, allogeneic hematopoietic stem cell transplantation; BM, bone marrow; CSA, cyclosporine; Flu/Treo, fludarabine/treosulfan; G-CSF, granulocyte colony-stimulating factor; GI, gastrointestinal; GIS, gastrointestinal system; GVHD, graft versus host disease; MNGIE, mitochondrial Neurogastrointestinal Encephalomyopathy; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; MTX, methotrexate; PBSC, peripheric blood stem cell; TYMP, thymidine phosphorylase; VOD, veno-occlusive disease.

1 | INTRODUCTION

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is caused by pathological mutations in the thymidine phosphorylase gene (*TYMP*) located on chromosome 22q13.33 and results in the accumulation of the thymidine (dThd) and deoxyuridine (dUrd) substrates, deoxyribonucleotide pool imbalance. This leads to impairment of mitochondrial DNA (mtDNA) replication, resulting in mtDNA depletion, multiple deletions, and point mutations.[1,2] MNGIE is an ultra-rare condition, characterized by severe gastrointestinal (GI) and neurological symptoms including GI dysmotility, cachexia, ptosis, ophthalmoparesis, or both, peripheral neuropathy and leukencephalopathy.[3] The outcome of the syndrome is fatal, and death usually occurs before the age of 40 years, although mild/atypical phenotypes have been reported.[3] There are no established therapeutic options for patients with MNGIE. Conventional hemodialysis and erythrocyte-encapsulated thymidine phosphorylase infusions, have shown to temporary decrease plasma dThd and dUrd concentrations.[4,5] Currently, the only effective permanent treatment is allogeneic hematopoietic stem cell transplantation (AHSCT), which permanently restores thymidine phosphorylase activity and eliminates circulating toxic levels of dThd and dUrd.[6] However, AHSCT is still associated with high mortality in MNGIE patients.[7] The number of transplanted patients reported in the literature is limited. We report here a retrospective evaluation s of four patients with MNGIE who underwent AHSCT.

2 | MATERIAL AND METHODS

We retrospectively evaluated patients who underwent stem cell transplantation with a diagnosis of MNGIE at Izmir Ege University Pediatric Bone Marrow Transplantation Center. Between January 2018 and December 2022, six AHSCT procedures were performed in four patients with MNGIE. Clinical features, mutation analysis, laboratory findings, and treatment of patients before stem cell transplantation were examined. Mutation analyzes were performed with *TYMP* gene sequencing. The pretransplant disease findings of the patients are summarized in Table 1. Performance scores, conditioning regimens, donor characteristics, stem cell sources, engraftment characteristics, posttransplant complications, and long-term follow-up of transplant patients were evaluated. Chimerism analysis was evaluated by examining DNA sequences with tandem repeats (STR) using the molecular PCR technique. Transplant characteristics of the patients are summarized in Table 2. Additionally, all cases were reviewed in detail. Autologous peripheral blood stem cell (PBSC) collection was performed in all cases as a backup for engraftment failure. We present here a clinical evaluation of four patients with MNGIE who underwent AHSCT and compare our findings with data in the literature.

2.1 | Case 1

The female patient, who had recurrent diarrhea and pseudo-obstruction signs, was diagnosed with MNGIE at the age of 15 years. *TYMP-1* mutation analysis of the patient showed homozygous p.P131L (c.392C>T) mutation. She had a severe cachectic appearance (body weight standard deviation score = −4.65), bilateral ptosis, hypertrichosis, clubbing and drop foot. Deep tendon reflexes could not be obtained in the lower extremities. The patient was diagnosed with Type 1 Diabetes mellitus two years before the diagnosis of MNGIE and was using an insulin pump. Grade III hepatic steatosis, sensorineural hearing loss, sensorineural myopathy, and leukoencephalopathy demonstrated by cranial magnetic resonance imaging (MRI) scan were other major clinical findings (Table 1). AHSCT was performed when the patient was 18.5 years old. The donor was a fully matched male cousin who was also a heterozygous carrier of MNGIE. The source of stem cells was granulocyte colony-stimulating factor (G-CSF)-stimulated bone marrow (BM) + PBSC. The myeloablative conditioning regimen was reduced intensity/toxicity using fludarabine/treosulfan (Flu/Treo), and antithymocyte globulin (ATG). Graft versus host prophylaxis was performed with cyclosporine (CSA)+ short course methotrexate (MTX) (Table 2). Defibrotide was used for veno-occlusive disease (VOD) prophylaxis. The patient started on a high protein/fat and low carbohydrate (ketogenic diet) before the transplant and continued the same diet throughout the transplant (details of the diet in MNGIE is to be reported in a separate paper). Neutrophil (absolute neutrophil count; ANC) and platelet engraftment occurred on days 12 and 15 after HSCT, respectively. Gram-negative bacterial sepsis and adenovirus gastroenteritis occurred in the posttransplant follow-up, which was successfully treated. Acute graft versus host disease (GVHD) did not develop. She was discharged from hospital 57 days after transplant. Chimerism in the first month was 100%, and follow-ups showed full chimerism. After transplantation, the plasma thymidine level was below the level of analysis detection. The patient's need for insulin therapy was decreased. She started menstruating 19 months after HSCT. The patient's most recent follow-up was 50 months after transplantation. The patient feeds totally by mouth, with no requirement for total parenteral nutrition (TPN) and without vomiting attacks. On neurological examination, the sensory responses are improved in the upper extremity, although the demyelination findings are still present in the lower extremity. The patient has not been hospitalized for three years and has started university education. There is no evidence of chronic GVHD; she is followed with fully donor chimerism.

2.2 | Case 2

Patient 2 was followed up with recurrent attacks of diarrhea, inability to gain weight and hepatomegaly since infancy. With the detection of

TABLE 1 Pretransplant clinical characteristics of MNGIE patients

Patient	Gender	Age of diagnosis (year)	TYMP mutation	Thymidine (μmol/L)	2′-Deoxy uridine (μmol/L)	Weight at HSCT (kg) (SD per age)/BMI	PFS (%)	GI symptoms	TPN	Neurologic findings	Cranial MRI	Endocrinological findings
1	F	15	Homozygous p.P131L (c.392C>T)	0.17	0.44	35 (−4.65)/13.6	70	Cachexia diarrhea, borborygmi, vomiting, pseudo-obstruction	Yes	Demyelinating peripheral neuropathy, sensory neural deafness, absent deep tendon reflexes, bilateral ptosis	Leukoencephalopathy, hyperintense foci in the parietooccipital cerebral white matter	Type 1 DM—insulin dependent, primary amenorrhea
2	M	18	Homozygous p.P131L (c.392C>T)	8.54	9.86	45 (−3.4)/13.4	80	Cachexia diarrhea, Pangastrit bulbit	No	Sensory neural axonal neuropathy, sensory neural deafness, ptosis	Leukoencephalopathy, hyperintense foci in the parietooccipital cerebral white matter	Prediabetic
3	M	12	Homozygous p.P131L (c.392C>T)	–	–	19 (−7.0)/11.2	60	Cachexia diarrhea, vomiting, pseudo-obstruction	Yes	Demyelinating polyneuropathy, bilateral foot drop, sensory neural deafness, absent deep tendon reflexes, mild ptosis	Hyperintense foci in the parietooccipital cerebral white matter	Prediabetic
4	F	17	Homozygous c.215G>A (p.G72E)	–	–	28 (−7)/10	60	Cachexia diarrhea, borborygmi, subileus	Yes	Demyelinating polyneuropathy, bilateral foot drop, distal paresthesias, areflexia, cognitive impairment	Hyperintense foci in the cerebral white matter	Primary amenorrhea

GI, gastrointestinal; HSCT, hematopoietic stem cell transplantation; PFS, performance score; SD, standard deviation; TPN, total parenteral nutrition; TYMP, thymidine phosphorylase.

TABLE 2 Transplantation characteristics of MNGIE patients

Tx no	Patient no	Age at HSCT	Donor	Donor mutation	ABO mis-match	Conditioning regimen	ATG-F (total dose)	GVHD prophylaxis	HSC source	Number of TNC	Number of CD34+ cells/ CD3+ cells	Engraft. ANC > 500/μl on day	Engraft. PLT > 20,000/ μl on day	Chimerism 1st month	Chimerism 3rd month	Outcome
1	1	18 years 9 month	MFD	Heterozygous p.P131L (c.392C>T)	Minor	FLU (150 mg/kg) TREO (42 g/m^2)	35 mg/kg	CSA/MTX	BM + PBSC	8.20×10^8/kg	5.0×10^6/kg 0.9×10^8/kg	12	15	100	100	Fully chimeric, no acute or chronic GVHD, decreased insulin requirement; Neurologic improvement on upper extremities, fully oral feeding, slight weight gain
2	2	20 years 1 month	MSD	Heterozygous p.P131L (c.392C>T)	Absent	FLU (150 mg/kg) TREO (42 g/m^2)	30 mg/kg	CSA/MTX	BM + PBSC	6.3×10^8/kg	7.8×10^6/kg 1.1×10^8/kg	13	17	100	–	Exitus on day 72 after HSCT because of acute Grade IV GIS GVHD
3	1 (1st HSCT)	14 years	Haplo, MFD	Absent	Absent	FLU (150 mg/kg) TREO (36 g/m^2)	30 mg/kg	Posttx CYC/ Tacro/ Pred	BM + PBSC	12.9×10^8/kg	9.3×10^6/kg 1.3×10^8/kg	14	13	85	0	Secondary graft failure, autologous stem cell backup was made and second transplant was done
4	3 (2nd HSCT)	14 years 6 month	Haplo, MFD	Absent	Absent	FLU/(150 mg/kg) CYC 14.5 mg/kg × 2 days TBI 1 × 2 Gy	30 mg/kg	Posttx CYC/ Tacro/ Pred	PBSC	29×10^8/kg	16×10^6/kg 0.77×10^8/kg	–	–	0	0	Primary graft failure, exitus on 10 months after HSCT with disease progression
5	4 (1st HSCT)	18 years 8 month	MUD 10/10	Absent	Major	FLU (150 mg/kg) TREO (36 g/m^2)	30 mg/kg	CSA/MTX	BM	2.4×10^8/kg	1.5×10^6/kg 0.14×10^8/kg	15	17	72	10	Secondary graft failure, disease symptoms persist, preparing second HSCT
6	4 (2nd HSCT)	19 years	MUD 10/10	Absent	Major	FLU (150 mg/kg) Busulfan (3.8 mg/kg/g × 4 days)	30 mg/kg	CSA/MTX	BM	2.12×10^8/kg	2.86×106/kg 0.4×10(/kg)	–	–	0		Primary graft failure, autologous stem cell backup was made. Following with MNGIE

ATG, antitimosit globulin; BM, bone marrow; Csa, cyclosporine; CYC, cyclophosphamide; Flu/Treo, fludarabine/treosulfan; GIS, gastrointestinal system; GVHD, graft versus host disease; Haplo, haploidentical; MFD, matched family donor; MSD, matched sibling donor; Mtx, methotrexate; MUD, matched unrelated donor; PBSC, periferic blood stem; Pred, prednisolon; Tacro, tacrolimus; TBI, total body irradiation.

homozygous p.P131L (c.392C>T) mutation in the *TYMP-1*gene, he was diagnosed with MNGIE at 18 years of age. Examination before HSCT revealed cachexia, hepatomegaly, hepatosteatosis, bilateral ptosis, sensorineural hearing loss, and polyneuropathy. Brain MRI showed diffuse periventricular and bilateral parietooccipital white matter changes (Table 1). The patient underwent AHSCT at the age of 20 years. The donor was 10/10-matched sister, who was a heterozygous carrier of MNGIE. The conditioning regimen included Flu/Treo and ATG, and for GVHD prophylaxis, CSA+MTX was administered. Defibrotide was used for VOD prophylaxis. The source of stem cells was G-CSF stimulated BM+PBSC. Neutrophil engraftment occurred on day 13 after HSCT, and platelet engraftment on day 13 after HSCT. Donor chimerism was 100% 1 month after transplantation. Fifty days after stem cell transplantation, acute GVHD Stage IV gastrointestinal system(GIS) GVHD developed without liver and skin involvement. The daily stool volume was >200 cc/kg/day, and severe bloody diarrhea and abdominal pain occurred. An endoscopy–colonoscopy of the patient was compatible with acute GVHD. A high-dose steroid + tacrolimus therapy was rapidly initiated, but without response. On day 74 after HSCT, the patient died due to steroid-resistant GIS GVHD and massive GI bleeding (Table 2).

2.3 | Case 3

Patient 3 was diagnosed with MNGIE at 12 years of age. He had severe vomiting attacks (around 1500 ml per day) and had classical MNGIE symptoms including cachexia, sensorineural hearing loss, polyneuropathy, bilateral foot drop, and loss of deep tendon reflexes in the lower extremities (Table 1). *TYMP-1* mutation analysis showed a homozygous p.P131L (c.392C>T) mutation. No matched tissue type donor was found for the patient. At the age of 14 years, the patient underwent ASCT from his haploidentical uncle who was not a carrier of the disease. The conditioning regimen included ATG 30 mg/kg (−10,−9,−8) /Flu 150 mg/kg (−7,−6,−5,−4,−3)/Treo 36 gr/m^2 (−7,−6,−5). Cyclophosphamide 50 mg/kg/day (+3,+4), Mesna 200% dose, Tacrolimus and prednisolone were used for GVHD prophylaxis. G-CSF stimulated BM+PBCS were used as the source of stem cells. No complications developed during and after the conditioning regimen. Neutrophil engraftment occurred on day 14 after HSCT, and platelet engraftment on day +13. Acute GVHD did not develop. Donor chimerism was 85%, 1 month after transplantation; however, this declined to 0% 3 months after transplantation. Secondary engraftment failure developed and an autologous stem cell backup was performed due to pancytopenia. A second stem cell transplant was performed with the same haploidentical donor 6 months after the first HSCT. The second conditioning regimen was a non-myeloablative haploidentical (Baltimore) protocol using only PBSC as the stem cell source. The patient's donor chimerism was 0% in the 1st month after transplantation, and the patient was considered a primary engraftment failure. The patient's MNGIE symptoms persisted, and he died from disease progression 16 months posttransplant (Table 2).

2.4 | Case 4

The patient had recurrent diarrhea-vomiting episodes, weight loss and muscle weakness since the age of 7 years and was diagnosed with MNGIE at 17 years of age. *TYMP-1* mutation analysis showed a homozygous c.215G>A (p.G72E) mutation. The clinical complaints of the patient were mainly secretory diarrhea, severe abdominal pain, signs of pseudo-obstruction, and muscle weakness. Physical examination revealed bilateral ptosis, bilateral drop foot, contracture deformity in the ankles, clubbing, and hepatomegaly (Table 1). AHSCT was performed at the age of 18.5 years. The donor was a 10/10 matched-unrelated donor. The conditioning regimen was reduced toxicity (Flu/Treo/ATG) and GVHD prophylaxis was with CSA+MTX. Defibrotide was administered for VOD prophylaxis. The source of stem cells was BM. Due to the major ABO blood group mismatch, erythrocyte depletion in the BM product was accomplished using an automated method. White blood cell engraftment occurred at day +15, platelet engraftment at day 27 following transplant. During follow-up, no severe infection or acute GVHD were observed. Chimerism was found at 72% in the first month after the HSCT, but decreased to 10% in the 3rd month after transplantation. Secondary engraftment failure developed. Six months after the first transplant, a second stem cell transplantation was made from the same donor. The conditioning regimen was busulfan-based and the stem cell source was again BM. However, after the second transplantation procedure, primary engraftment failure developed. The patient's cytopenia continued, so on the 45th posttransplant day, an autologous stem cell infusion was made. Neutrophil engraftment occurred on the 14th day after autologous stem cell infusion. Patient follow-up shows repeated ileus attacks, inability to feed, vomiting, and severe neuropathy findings (Table 2).

3 | DISCUSSION

AHSCT is a well-defined treatment option for MNGIE[8–10] and is effective in permanently restoring the biochemical imbalances.[11] It requires chemotherapy and immunosuppressive therapy and is associated with a high risk for complications and mortality related to therapy, including GVHD.[6] In this retrospective study, we report the clinical experience on this procedure at our center.

A total of six transplantation procedures were performed for four patients. In the study published by Kalkan Uçar et al. in 2022, patients diagnosed with MNGIE at Ege University Faculty of Medicine, Department of Pediatrics, Department of Pediatric Metabolism and Nutrition were evaluated.[12] In this patient group, we performed AHSCT on four patients. Three patients of these patients had a homozygous p.P131L (c.392C>T) *TYMP* mutation, and one patient had a homozygous p.G72E (c.215G>A) mutation. We concluded that the "Mediterranean"/homozygous p.P131L (c.392C>T) mutation is associated with a rapidly progressive clinical course and poor prognosis.[12] The mean age at diagnosis of our patients was 16.4 years and all patients had

persistent GI manifestations and neurological deficit findings at the time of diagnosis. Rapid progression was the major clinical observation outcome in our patient cohort. It is well described in the literature that transplantation before the development of permanent GI symptoms can increase the success of transplantation.[6,13]

The first allogeneic transplant in MNGIE was performed by Hirano et al. on two patients and in this study there was evidence of improvement in biochemical abnormalities.[9] The first multicenter study, evaluating 24 MNGIE patients undergoing AHSCT reported a survival rate of 37.5% after a median follow-up of almost 4 years.[7] The number of patients with MNGIE who are transplanted is still limited.[13,14,15] Nevertheless, HSCT is effective in the long term in improving quality of life, although it is limited by the high posttransplant mortality rate (63%) in severely symptomatic adult patients.[7]

Engraftment failure and GVHD have been determined as the most critical problems in MNGIE transplants.[7] Therefore, it has been reported that HSCT should be considered in pediatric patients and young adults with mild or no GI symptoms.[6] The mean age of our group at the time of transplantation was 17.9 years old, and all of them had severe permanent GI symptoms before transplantation. HSCT-related complications are more expected in younger adults with advanced disease. However, allogenic transplantation was successful in our 18.5-year-old patient (patient 1) with advanced GIS findings. She did not develop any transplant-related complications, and a significant improvement was achieved in her quality of life Therefore, we think the indication for transplantation in advanced disease can be evaluated on a patient basis.

It is recommended to use a fully compatible donor for stem cell transplantation in MNGIE.[10] The donors of our three patients, two of them from family members, were fully matched donors. Haploidentical stem cell transplantation was performed in a patient whose GI and neurological symptoms were severe, despite his young age, because a fully matched donor could not be found. Unmanipulated BM and peripheral stem cells were used as a source. Chemotherapy-related toxicity did not develop in patient who received a treo-based conditioning regimen with posttransplant cyclophosphamide. However, our patient, the first reported case of haploidentical stem cell transplantation, developed engraftment failure twice. The patient died of disease progression after autologous stem cell backup.

In the consensus report published in 2011, it was recommended to use BM as a source of stem cells.[10] We employed BM in five of the six transplants as a stem cell source and in three transplants, supplemented these with PBSCs. The consensus report also recommended a fludarabine/busulfan conditioning regimen.[10] In most cases, this conditioning regimen experience has been published, and has been shown to be associated with an increased toxicity in this patient group. Due to our patients developing severe GI and neurological deficits prior to transplantation, we aimed to reduce the toxicity of the conditioning regimen. By employing a treo-based regimen in five transplantation procedures. A second transplant for a patient with secondary engraftment failure was performed with a busulfan-based conditioning. One of patients is currently being followed up and has shown no severe organ toxicity or GVHD 50 months after transplantation (patient 1). Patient 1 now feeds totally by mouth, with a significant decrease in subileus attacks and improvement in her upper extremity on neurological examination. The patient's quality of life has improved sufficiently to embark on a university education. One patient died with acute Grade IV GIS GVHD early on in the posttransplantation period (patient 2). Engraftment failure developed in two patients, one of whom had a haploidentical transplant (patients 3 and 4). Experience with a treo-based preparation regimen at MNGIE, was first reported in the study of Zaidman et al.[13] Similar to our study, they reported engraftment failure in two of four patients. They reported that a reduced intensity/toxicity conditioning is not sufficient for this group of patients.[13] In our study, although the number of patients was limited, the treo-based regimen toxicity was also low in this patient group. However, this conditioning regimen may lead to engraftment failure. Therefore, we support the busulfan-based conditioning regimen, particularly in patients without severe organ toxicity. The addition of thiotepa to the treosulfan-based regimen is also debatable in the patient group with severe organ involvement.

AHSCT is still the only curative treatment option for MNGIE syndrome. In conclusion, based on our clinical experience, we retrospectively evaluated the transplantations performed at our center using a treosulfan-based reduced toxicity conditioning regimen. We also report on our experience with haploidentical transplants, the first reported case in the literature. Although the number of cases is limited, it is the treosulfan-based regimen is well tolerated. However, engraftment failure with this conditioning regimen is a significant problem. As previously reported in consensuses, early transplantation with the most compatible donor, without the development of permanent severe GIS symptoms, is vital for increasing the success of transplantation in MNGIE.

FUNDING

No external funding was received for this study.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest.

ORCID

Gülcihan Ozek https://orcid.org/0000-0001-7111-4214
Yeşim Oymak https://orcid.org/0000-0002-6908-8309

References

1. Filosto M, Cotti Piccinelli S, Caria F, et al. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE-MTDPS1). *J Clin Med*. 2018;7(11):E389. doi: 10.3390/jcm7110389
2. Hirano M, Nishigaki Y, Martí R. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): a disease of two genomes. *Neurologist*. 2004;10:8-17.
3. Filosto M, Scarpelli M, Tonin P, et al. Pitfalls in diagnosing mitochondrial neurogastrointestinal encephalomyopathy. *J Inherit Metab Dis*. 2011;34:1199-1203.
4. Röeben B, Marquetand J, Bender B, et al. Hemodialysis in MNGIE transiently reduces serum and urine levels of thymi- dine and deoxyuridine, but not CSF levels and neurological function. *Orphanet J Rare Dis*. 2017;12:1-4.

5. Bax BE, Levene M, Bain MD, et al. Erythrocyte encapsulated thymidine phosphorylase for the treatment of patients with mitochondrial Neurogastrointestinal Encephalomyopathy: study protocol for a multi-centre, multiple dose, open label trial. *J Clin Med*. 2019;8(8):1096.
6. Hirano M, Carelli V, De Giorgio R, et al. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): position paper on diagnosis, prognosis, and treatment by the MNGIE International Network. *J Inherit Metab Dis*. 2021;44(2):376-387. doi: 10.1002/jimd.12300
7. Halter JP, Michael W, Schüpbach M, et al. Allogeneic haematopoietic stem cell transplantation for mitochondrial neurogastrointestinal encephalomyopathy. *Brain*. 2015;138(10):2847-2858. doi: 10.1093/brain/awv226
8. Yadak R, Sillevis Smitt P, van Gisbergen MW, van Til NP, de Coo IFM. Mitochondrial neurogastrointestinal encephalomyopathy caused by thymidine phosphorylase enzyme deficiency: from pathogenesis to emerging therapeutic options. *Front Cell Neurosci*. 2017;11. doi: 10.3389/fncel.2017.00031
9. Hirano M, Martí R, Casali C, et al. Allogeneic stem cell transplantation corrects biochemical derangements in MNGIE. *Neurology*. 2006;67(8):1458-1460. doi: 10.1212/01.wnl.0000240853.97716.24
10. Halter J, Schüpbach WMM, Casali C, et al. Allogeneic hematopoietic SCT as treatment option for patients with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): a consensus conference proposal for a standardized approach. *Bone Marrow Transplant*. 2011;46(3):330-337. doi: 10.1038/bmt.2010.100
11. Sicurelli F, Carluccio MA, Toraldo F, et al. Clinical and biochemical improvement following HSCT in a patient with MNGIE: 1-year follow-up. *J Neurol*. 2012;259(9):1985-1987. doi: 10.1007/s00415-012-6500-z
12. Kalkan Uçar S, Yazıcı H, Canda E, et al. Clinical spectrum of early onset "Mediterranean" (homozygous p.P131L mutation) mitochondrial neurogastrointestinal encephalomyopathy. *JIMD Rep*. 2022;63(5):484-493. doi: 10.1002/jmd2.12315
13. Zaidman I, Elhasid R, Gefen A, et al. Hematopoietic stem cell transplantation for mitochondrial neurogastrointestinal encephalopathy: a single-center experience underscoring the multiple factors involved in the prognosis. *Pediatr Blood Cancer*. 2021;68(5):e28926. doi: 10.1002/pbc.28926
14. Peedikayil MC, Kagevi EI, Abufarhaneh E, Alsayed MD, Alzahrani HA. Mitochondrial neurogastrointestinal encephalomyopathy treated with stem cell transplantation: a case report and review of literature. *Hematology/Oncology and Stem Cell Therapy*. 2015;8(2):85-90. doi: 10.1016/j.hemonc.2014.12.001
15. Hanbali A, Rasheed W, Peedikayil MC, Boholega S, Alzahrani HA. Mitochondrial neurogastrointestinal encephalomyopathy syndrome treated with stem cell transplant: a case series and literature review. *Exp Clin Transplant*. 2018;16:773-778.

How to cite this article: Ozek G, Aksoylar S, Uçar SK, et al. Hematopoietic stem cell transplantation with reduced toxicity conditioning regimen in mitochondrial neurogastrointestinal encephalopathy syndrome. *Pediatr Blood Cancer*. 2023;e30334. https://doi.org/10.1002/pbc.30334