Prophylactic Allogeneic Hematopoietic Stem Cell Therapy for *CSF1R*-Related Leukoencephalopathy

Recently, Tipton and coworkers[1] reported on the results of allogeneic hematopoietic stem cell therapy (HSCT) in 7 individuals with *CSF1R*-related leukoencephalopathy. HSCT appeared to slow progression in most of them after about 6 months. An unresolved question is whether presymptomatic HSCT prevents the development of leukoencephalopathy in patients with pathogenic *CSF1R* variants or ameliorates the course if leukoencephalopathy subsequently develops.

We report the results of prophylactic HSCT in a 31-year-old woman who is heterozygous for the pathogenic *CSF1R* variant NM_005211.3(CSF1R): c.1754-2A>G previously detected in her family. She is the daughter of NO-2 in the report by Rademakers et al[2] (Fig 1) and was clinically and radiologically unaffected at presentation. All affected relatives had rapidly devastating disease, resulting in death within 3 years of diagnosis.

Given the uniformly fatal outcome in her relatives, the woman requested HSCT, based on previous case reports.[3-5] HSCT was discussed at length with her and her family. The decision to provide treatment followed multiple rounds of discussion among neurologists, hematologists, and geneticists nationally, as well as consultation with expertise from France and the United States. HSCT was performed in August 2020, using the Mayo Clinic reduced intensity conditioning regimen[1] with a 9/10 HLA-matched unrelated male donor bone marrow graft. Post-transplantation she received cyclophosphamide, sirolimus, and mycophenolate as graft versus host disease (GvHD) prophylaxis without pretreatment to open the blood–brain barrier. Engraftment was observed at day +20, and complete donor chimerism reached at day +27. Lumbar puncture at +12 months showed 99% donor chimerism in the cerebrospinal fluid; T-cells, B-cells, and monocytes were defined by morphology and flow cytometry. During the first 12 months post-transplantation, there were no manifestations of GvHD.

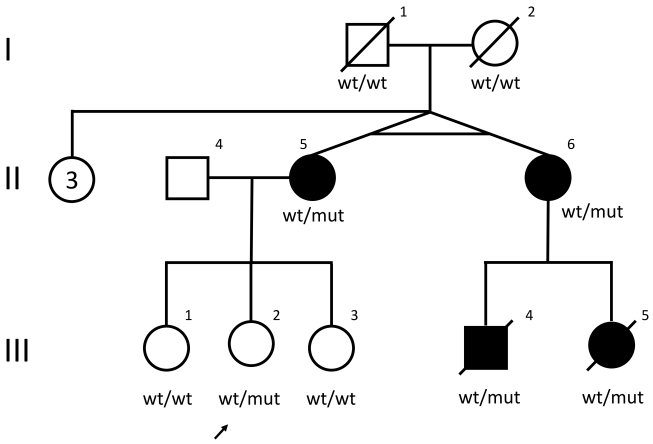

FIG 1. Pedigree of the Norwegian family with *CSF1R*-related leukoencephalopathy. Symbols: ● = affected female, ○ = unaffected female, ■ = affected male, □ = unaffected male, / = deceased individual, wt/wt = homozygous for wild-type (normal) *CSF1R* allele, wt/mut = heterozygous for pathogenic *CSF1R* variant. Arrow points to individual III:2, recipient of prophylactic HSCT. Monozygotic twins II:5 and II:6 are NO-2 and NO-1, respectively, in Rademakers et al.[2] Cause of death in all affected individuals was *CSF1R*-related leukoencephalopathy: II:5 died at age 40 years, II:6 at age 41 years, III:4 at age 36 years, and III:5 at age 31 years.

Clinical neurologic testing was unremarkable before HSCT and at +12 months. Cerebral magnetic resonance imaging (MRI) at −28, −11, −4, −3, and 0 months before HSCT was normal and remained so at +4, +8, and +12 months. Detailed neuropsychological testing performed at −5 months and repeated at +12 months was unremarkable.

One year after transplantation, the woman became subacutely ill. Her MRI was compatible with inflammation of the left temporal lobe, brainstem, medulla, and meninges. Mild pleocytosis was present in the cerebrospinal fluid, but no infectious agents were detected, and there was no evidence of malignancy or autoimmune disease despite extensive investigations. An allogeneic immunological reaction seems a probable but unproven cause. Clinically, she was mildly affected with subtle signs of myelopathy and modest cognitive difficulties. She improved spontaneously without medical intervention.

To our knowledge, this is the first report of allogeneic HSCT performed with the aim of preventing progressive, potentially fatal *CSF1R*-related leukoencephalopathy in an asymptomatic individual. At +17 months, evidence of leukoencephalopathy is absent. This is encouraging but is, of course, not proof of efficacy. The decision to provide HSCT was ethically challenging. We remain uncertain as to whether asymptomatic individuals with pathogenic *CSF1R* variants should be provided HSCT. Bridging therapies that could stem the progression of leukoencephalopathy,[6] so that HSCT is delayed until MRI changes develop, might be a better option.

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Reply to "Prophylactic Allogeneic Hematopoietic Stem Cell Therapy for *CSF1R*-Related Leukoencephalopathy"

We congratulate Horn and colleagues on being the first to successfully administer hematopoietic stem cell transplantation (HSCT) to an asymptomatic carrier of a pathogenic *CSF1R* variant.[1]

Our recent paper[2] adds to the growing body of literature supporting HSCT as a disease-modifying therapy with the ability to stabilize and even improve the neurological function of patients with CSF1R-related leukoencephalopathy (CSF1RL). Although this is an exciting advancement in the field, heterogeneity of clinical outcomes with HSCT demonstrates that we currently do not know which patients are the best candidates for HSCT. Based on our work and the work of others, we present a hypothetical model for CSF1RL progression and propose the optimal treatment window for HSCT (Fig. 1).

Current literature best informs when the treatment window for HSCT in CSF1RL has closed. Within our series, patient 2 was one of the most severely affected individuals (clinical symptoms and magnetic resonance imaging changes)[3] during transplant. Follow-up at 20 months demonstrated a continued, albeit slowed, rate of clinical and radiographic progression. We suspect that HSCT earlier in the disease course portends a better prognosis as illustrated by our patient 4.[2] Thus, patients will likely have the best clinical outcomes if HSCT is administered while they are in the prodromal to early-moderate stages of symptomatic disease (Fig. 1).

Horn and colleagues were presented with a unique, likely to recur, decision-making process on how early HSCT can be performed. Given the rapidly progressive nature of CSF1RL, early symptomatic or even presymptomatic treatment is expected to provide the greatest benefit. We suggest that a carrier of a pathogenic *CSF1R* variant who is experiencing first signs of symptomatic disease, clinically, radiologically, or both, is probably the best candidate for HSCT. Asymptomatic *CSF1R* variant carriers are usually identified because of their family relationship to a person with symptomatic CSF1RL. These individuals should be followed closely to identify the earliest evidence of symptom onset. As demonstrated by the case of Horn et al.,[1] we presently do not recommend prophylactic HSCT for asymptomatic carriers because *CSF1R* pathogenic variants have high but incomplete penetrance.[4]

CSF1RL is associated with reduced blood–brain barrier (BBB) permeability[5]; however, it is unclear how much disease progression is necessary for transplanted microglial precursor cells to efficiently traverse the BBB. HSCT pretreatment to increase BBB permeability can be administered; however, the case presented by Horn and colleagues achieved more than 99% donor chimerism in cerebrospinal fluid (CSF) without pretreatment. This suggests sufficient BBB permeability, presumably from the emerging leukoencephalopathy, despite the absence of clinical or radiographic disease manifestations, that is, presymptomatic. Nevertheless, confidence that *CSF1R* variant carriers are truly "presymptomatic" is based only on penetrance probabilities, and there is a need for reliable disease biomarkers. A recent study found elevated serum and CSF neurofilament light (NfL) chain in asymptomatic *CSF1R* mutation carriers.[6] NfL levels could equip clinicians for determining whether an asymptomatic carrier is "presymptomatic" if appropriate cutoff values are determined. Then, it would be reasonable to discuss prophylactic HSCT with presymptomatic *CSF1R* pathogenic variant carriers. ■

Key Words: *CSF1R*-related leukoencephalopathy; stem cell transplantation; genetics; treatment

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