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To the editor:

Efficacy of hematopoietic cell transplantation in metachromatic leukodystrophy: the Dutch experience

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Metachromatic leukodystrophy (MLD) is a neurodegenerative disorder caused by deficiency of arylsulfatase A, leading to sulfatide accumulation and subsequent demyelination of the central and peripheral nervous system.1,2

MLD is divided into 3 subtypes, based on the age of onset: late-infantile (<30 months), juvenile (2.5-16 years), and adult (>16 years). With early disease onset, progression is fast and motor signs are prominent, in contrast to later forms with insidious onset of cognitive deterioration.3 Eventually, all acquired skills are lost and patients die. Hematopoietic cell transplantation (HCT) is a possible treatment, but systematic outcome data are lacking, due to the use of different eligibility criteria and protocols worldwide.4-12 In order to assess HCT efficacy, we evaluated all 35 consecutive MLD patients presenting between 2004 and 2015 in our department, the Dutch Leukodystrophy Referral Center (Figure 1A).

Patients with a total intelligence quotient (IQ) above 70 and without gross neurological signs (ie, ambulation without support, no dysphagia) were considered HCT candidates (Tables 1 and 2). HCT was performed at the University Medical Center Utrecht (UMCU; Blood and Marrow Transplantation Program) according to international protocols.13 Patients received HCT from either a HLA identical sibling (n = 3; noncarrier) or an unrelated umbilical cord blood (n = 10) donor (with a minimum match of 4 of 6 HLA loci) after fludarabine (160 mg/m²) plus busulfan (targeted to cumulative exposure of 90 mg × h/L); thymoglobuline was added in cord blood recipients. For details, see supplemental Methods (available on the Blood Web site).

Transplanted patients were followed for a mean duration of 4.7 years; assessments included neurological examination, cognitive function, brain magnetic resonance imaging (MRI) rated by the MLD-Loes score,14 measurement of arylsulfatase A activity, and assessment of nerve conduction velocity. Gross motor function (GMF) was scored according to a classification developed for MLD.15 After 5 years, follow-up intervals were adapted to clinical status. Follow-up of nontransplanted patients (mean, 4.6 years) consisted of neurological examination, in some cases, assessment of nerve conduction velocity, and MRI, the intervals depending on clinical condition. Two composite survival end points were analyzed: intervention-free survival (IFS) and activities of daily living-compromise-free survival (AFS).

There was no transplantation-related mortality. All patients engrafted and achieved full donor chimerism. Three symptomatic patients (23%; 1 late-infantile, 1 juvenile, 1 adult) died due to disease progression, all within 1 year after HCT. Eight nontransplanted patients (36%) died 22 to 72 months after diagnosis. Overall survival at latest assessment was 76.9% for transplanted and 63.6% for nontransplanted patients (Figure 1B). One patient experienced acute, 3 chronic graft-versus-host disease (1 extensive). All were effectively
successfully treated with corticosteroids and came off of immuno-
suppressive therapy.

IFS (whereby death, wheelchair dependency, gastrostomy, and
intrathecal baclofen treatment were regarded as events) was 69.2%
for transplanted and 9.1% for nontransplanted patients ($P = .03$;
Figure 1C). Symptomatic transplanted patients had lower estimated
IFS (42.9%) than presymptomatic transplanted patients (100%)
at HCT ($P = .052$; Figure 1D). AFS was defined as no occur-
rence of death, motor (clinically relevant peripheral neuropathy,
spasticity or ataxia, gross motor function $\geq$3), or cognitive (IQ decline
$\geq$6 points) deterioration. Transplanted patients had higher AFS
(46.2%) than nontransplanted patients (0%; $P = .01$; Figure 1C).

![Figure 1. Patient cohort and outcome after HCT.](image)

(A) Thirteen transplanted patients (magenta shades, 6 asymptomatic [diagnosed because of an affected sibling]; mean age, 14.4
years; range, 2-35 years) and 22 nontransplanted patients (blue shades; mean age, 6.5 years; range, 2-32 years). Four patients were referred from other European countries
(Belgium, Denmark, and Luxembourg); the remainder came from The Netherlands. (B) Overall survival probability for transplanted and nontransplanted patients. (C) Probability of IFS
and AFS for transplanted and nontransplanted patients. (D) Probability of IFS and AFS for symptomatic (n = 7) and presymptomatic (n = 6) transplanted patients.

Table 1. Evolution with and without HCT: transplanted patients

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>MLD type</th>
<th>Follow-up since HCT, months</th>
<th>GMF pre-HCT</th>
<th>GMF post-HCT*</th>
<th>Cognition pre-HCT (age in years/months)</th>
<th>Cognition post-HCT (age in years)</th>
<th>MRI pre-HCT</th>
<th>MRI post-HCT*</th>
<th>Deceased (age in years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD-50</td>
<td>Late-infantile</td>
<td>10</td>
<td>2</td>
<td>6</td>
<td>DQ 105 (25 mo)</td>
<td>NA</td>
<td>2</td>
<td>20</td>
<td>Yes (3 y)</td>
</tr>
<tr>
<td>MLD-45</td>
<td>Late-infantile</td>
<td>60</td>
<td>2</td>
<td>5</td>
<td>DQ 101 (35 mo)</td>
<td>70 (4 y)</td>
<td>3</td>
<td>8</td>
<td>No</td>
</tr>
<tr>
<td>MLD-16</td>
<td>Juvenile</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>104 (6 y)</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>MLD-37</td>
<td>Juvenile</td>
<td>127</td>
<td>0</td>
<td>2</td>
<td>DQ 116 (26 mo)</td>
<td>95 (6 y)</td>
<td>2</td>
<td>4</td>
<td>No</td>
</tr>
<tr>
<td>MLD-4</td>
<td>Juvenile</td>
<td>112</td>
<td>1</td>
<td>1</td>
<td>110 (5 y)</td>
<td>56 (10 y)</td>
<td>4</td>
<td>8</td>
<td>No</td>
</tr>
<tr>
<td>MLD-53</td>
<td>Juvenile</td>
<td>11</td>
<td>1</td>
<td>6</td>
<td>74 (7 y)</td>
<td>NA</td>
<td>20</td>
<td>25</td>
<td>Yes (8 y)</td>
</tr>
<tr>
<td>MLD-14</td>
<td>Juvenile</td>
<td>61</td>
<td>1</td>
<td>1</td>
<td>94 (14 y)</td>
<td>93 (17 y)</td>
<td>12</td>
<td>11</td>
<td>No</td>
</tr>
<tr>
<td>MLD-21</td>
<td>Adult</td>
<td>27</td>
<td>0</td>
<td>0</td>
<td>100 (17 y)</td>
<td>95 (18 y)</td>
<td>10</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>MLD-30</td>
<td>Adult</td>
<td>94</td>
<td>0</td>
<td>1</td>
<td>104 (19 y)</td>
<td>107 (21 y)</td>
<td>7</td>
<td>11</td>
<td>No</td>
</tr>
<tr>
<td>MLD-41</td>
<td>Adult</td>
<td>77</td>
<td>0</td>
<td>0</td>
<td>91 (25 y)</td>
<td>89 (27 y)</td>
<td>12</td>
<td>13</td>
<td>No</td>
</tr>
<tr>
<td>MLD-15</td>
<td>Adult</td>
<td>59</td>
<td>0</td>
<td>0</td>
<td>87 (35 y)</td>
<td>73 (40 y)</td>
<td>11</td>
<td>14</td>
<td>No</td>
</tr>
<tr>
<td>MLD-51</td>
<td>Adult</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>61 (22 y)</td>
<td>NA</td>
<td>16</td>
<td>24</td>
<td>Yes (22 y)</td>
</tr>
<tr>
<td>MLD-2</td>
<td>Adult</td>
<td>62</td>
<td>0</td>
<td>0</td>
<td>72 (28 y)</td>
<td>76 (31 y)</td>
<td>13</td>
<td>12</td>
<td>No</td>
</tr>
</tbody>
</table>

DQ, developmental quotient; NA, not available.

*GMF and MRI post-HCT are scored at latest follow-up assessment.
Symptomatic transplanted patients had an AFS probability of 28.6%, vs 66.7% for presymptomatic transplanted patients \( (P = .11; \text{Figure 1D}). \)

The only surviving late-infantile patient had very limited motor function 3 years after HCT, due to progressive neuropathy. Motor function remained preserved in 2 of 4 surviving juvenile and 5 adult patients. Progressive neuropathy hampered motor function in 2 juvenile patients. Regarding the adult patients, none showed signs of spasticity or ataxia, and when present \( (n = 2) \), polyneuropathy was mild and did not interfere with motor function. In the entire transplanted group, nerve conduction remained normal in 1, stabilized in 8, and further decreased in 2 patients. In comparison, in the nontransplanted patients, all late-infantile and all 13 juvenile patients deteriorated from intact motor function within 16 months to hardly any remaining motor function. In only 2 patients (adult onset) did motor function remain intact for the duration of follow-up (Tables 1 and 2).

Cognitive function (Tables 1 and 2) remained unchanged in 6 transplanted patients. One late-infantile, 1 juvenile, and 1 adult patient showed clear cognitive deterioration after HCT. For the evaluable nontransplanted patients at diagnosis \( (n = 10) \), all IQs were low. At follow-up, cognition was not formally tested, but, clinically, patients continued to deteriorate.

Other neurological symptoms were more severe in nontransplanted patients. Epilepsy developed in half \( (11 \text{ of } 21; 52\%) \) vs 1 of 13 \( (8\%) \) of the transplanted group. Additionally, severe spasticity was a frequent problem in nontransplanted patients with 9 of 21 juvenile patients \( (43\%) \) needing intrathecal baclofen treatment. At latest assessment, 17 of 21 evaluable nontransplanted patients \( (81\%) \) required feeding via gastrostomy whereas only 1 transplanted patient (late-infantile) required gastrostomy 5 years after HCT. Brain MRI (Tables 1 and 2) improved in 5 of 10 surviving transplanted patients \( (50\%) \), after initial deterioration, and stabilized in the remainder. In all nontransplanted patients, but 1 adult, MRI deteriorated over time.

In summary, the unique characteristics of this study are the comparison of disease evolution in transplanted patients with the natural course of patients no longer eligible for HCT diagnosed within the same period. We used consistent decision guidelines, and all transplantations were performed in a single center. Our data show that, under these conditions, HCT is a safe procedure for pre- and early symptomatic MLD patients with the juvenile or adult type, resulting in disease stabilization and high disease burden-free survival, with even the suggestion of some brain repair, reflected by improvement of brain MRI abnormalities, confirming earlier findings.\(^{5,16–19}\) For late-infantile and more advanced patients, results are not encouraging, suggesting that HCT in those at best delays disease progression. Our study shows that motor and cognitive functions are good predictors of outcome. Clearly, affected motor (inability to walk without support) and cognitive (IQ below 75) function resulted in no benefit of HCT. Brain MRI abnormalities were more severe and extensive in the patients rejected for HCT than in successfully transplanted patients, suggesting that an MRI score above 15 is associated with an unsuccessful outcome. As HCT remains an intensive treatment and initial neurological worsening is to be expected, it should not be considered if the disease has progressed beyond a certain stage. In these patients, HCT negatively impacts their life and that of their families at a time that should be cherished before the inevitable frank disease progression sets in.

Limitations of our study are its retrospective character and the inevitable selection bias resulting from the fact that nontransplanted patients were more severely affected than the transplanted patients at diagnosis. In addition, some issues remain: 3 patients (2 with the juvenile form) showed cognitive deterioration, despite presymptomatic HCT, and despite relatively stable white matter changes, suggesting neuronal involvement perhaps less amenable to treatment with HCT. Peripheral nerve involvement seemed unaltered, despite normal circulating enzyme levels after transplantation. Lastly, especially for the slowly progressive adult forms, follow-up needs to be longer to fully evaluate effects of HCT.

As the best moment for HCT is as early as possible and before clinical disease onset, it is of utmost importance to test all siblings of an
index case, including older ones. For more advanced and late-infantile patients, results are discouraging. For the majority of patients evaluated, HCT was no longer an option, nor did they qualify for treatment trials, emphasizing the need for earlier diagnosis and better treatment strategies.

The online version of this article contains a data supplement.

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Contribution: N.I.W. and J.J.B. designed and coordinated the study; D.F.v.R. and N.I.W. wrote the first draft of the manuscript; J.J.B., P.M.v.H., and J.K. were responsible for HCT; D.F.v.R. and M.E.v.E. collected and analyzed data; K.J.O. established evaluation of cognitive function; P.J.W.P. performed MRI analyses; C.E.M.H. was responsible for follow-up of the adult patients; and N.I.W. provided expertise and were responsible for follow-up of all patients.; and all authors critically revised the manuscript for intellectual content, did a final review, and approved the manuscript.

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References


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