Full-Intensity Transplantation and Short Telomeres Increase the Risk of Cognitive Impairment after Allogeneic Hematopoietic Cell Transplantation (HCT)

Results of a Prospective Longitudinal Study

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Abstract 913 (Alysia Bosworth) Full-Intensity Transplantation and Short Telomeres Increase the Risk of Cognitive Impairment After Allogeneic Hematopoietic Cell Transplantation (HCT) – Results of a Prospective Longitudinal Study

Background

• Impaired cognition is an increasingly recognized concern after HCT
• Gaps in previous research
  – Cognitive functioning after reduced-intensity HCT
  – Healthy control comparison groups
  – Pathogenesis of cognitive impairment after HCT
• Current study addresses these gaps
  – Including patients with full and reduced-intensity HCT
  – Including a healthy control comparison group
  – Understanding the pathogenesis by testing the hypothesis that shorter telomeres could play a role in cognitive impairment after HCT
    • Telomeres are repetitive DNA-protein structures localized to chromosome ends that protect chromosome integrity
    • Telomeric shortening occurs with each cell division
    • Chemotherapy and radiation hastens telomeric attrition
    • Glial cells are mitotic and susceptible to telomere shortening
Study design & methods

- 2-year prospective, longitudinal study
  - 2-hour battery of standardized neurocognitive tests
    - 14 tests assessing 8 domains
    - Healthy control scores used to correct HCT patient scores for practice effects
  - Blood draw (DNA) pre-HCT
    - qPCR-based telomere assay to assess relative telomere length (ratio of telomeres to single genes)
    - Relative telomere length dichotomized as short vs. long at median value
  - Medical record abstraction and self-report
### Demographic & clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>HCT recipients</th>
<th>Healthy controls</th>
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</thead>
<tbody>
<tr>
<td><strong>Cohort size</strong></td>
<td>242</td>
<td>98</td>
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<tr>
<td><strong>Participants at 2-y time point</strong></td>
<td>125</td>
<td>45</td>
</tr>
<tr>
<td><strong>Age at HCT (median, range)</strong></td>
<td>49 (19-71)</td>
<td>51 (19-73)</td>
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<tr>
<td><strong>Males</strong></td>
<td>149 (62%)</td>
<td>53 (54%)</td>
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<tr>
<td><strong>Acute leukemia/MDS</strong></td>
<td>168 (69%)</td>
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<tr>
<td><strong>Full-intensity HCT conditioning</strong></td>
<td>116 (48%)</td>
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<td></td>
<td>FTBI + chemo</td>
<td>84 (72%)</td>
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<tr>
<td><strong>Reduced-intensity HCT conditioning</strong></td>
<td>126 (52%)</td>
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<tr>
<td></td>
<td>Fludarabine + melphalan</td>
<td>114 (90%)</td>
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<tr>
<td><strong>Unrelated donor</strong></td>
<td>141 (58%)</td>
<td></td>
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<tr>
<td><strong>Blood samples for telomere analysis</strong></td>
<td>142</td>
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</tbody>
</table>
Allogeneic HCT recipients have poorer cognitive functioning than healthy controls

- Executive function
- Processing speed
- Verbal fluency
- Fine motor dexterity
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HCT recipients vs. healthy controls

Executive function
(D-KEFS Color-Word Interference – Inhibition)

Adjusted for age, race, income

Healthy controls

HCT recipients

p = 0.0008
### Risk factors for poorer cognitive function

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<td>Hispanic ethnicity</td>
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<td>Low education</td>
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<td>X</td>
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<td>Low income</td>
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<td>High fatigue</td>
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<tr>
<td><strong>Full-intensity HCT</strong></td>
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<td><strong>X</strong></td>
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</tbody>
</table>
Patients receiving full-intensity conditioning are at risk for cognitive impairment as compared with reduced-intensity recipients

- Executive function
- Processing speed
- Verbal speed
- Visual memory

Patients receiving reduced-intensity conditioning are spared
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**Results**

**HCT intensity**

**Executive function**
(D-KEFS Color-Word Interference – Inhibition)

*Adjusted for age, income, diagnosis*

- Healthy controls
- RIC HCT recipients
- Full-intensity HCT recipients

$p = 0.13$
$p = 0.01$
Telomere length and cognitive functioning

Male HCT recipients: No association between telomere length and cognitive impairment

Female HCT recipients: Telomeric shortening prior to HCT is associated with poorer cognitive functioning after HCT
  - Executive function
  - Processing speed
  - Verbal speed
  - Working memory
Telomere length and cognitive functioning in female HCT recipients

Executive function
(D-KEFS Verbal Fluency – Category Switching)

HCT recipients with long telomeres
HCT recipients with short telomeres

Adjusted for age, race, income, IQ, diagnosis, risk of relapse, remission status

p = 0.004
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Summary

• **Allogeneic HCT recipients have poorer cognitive functioning than healthy controls**
  – Executive function, processing speed, verbal fluency, fine motor dexterity

• **Patients receiving full-intensity conditioning are at risk for having poorer cognitive functioning as compared with reduced-intensity recipients**
  – Executive function, processing speed, verbal speed, visual memory

• **Patients receiving reduced-intensity conditioning are spared**

• **Telomeric shortening prior to HCT is associated with poorer cognitive functioning after HCT in females**
  – Executive function, processing speed, verbal speed, working memory
Conclusions

- The study has identified vulnerable sub-populations that could benefit from multidisciplinary support
  - Older age
  - Male gender
  - Hispanic ethnicity
  - Low SES
  - High fatigue
  - Full-intensity allogeneic HCT recipients

- The study provides preliminary evidence for an association with telomere length and cognitive functioning