Case Report

Myelodysplasia and acute myeloid leukemia fifteen years after high-dose cyclophosphamide in a child with severe aplastic anemia

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A R T I C L E  I N F O

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Introduction

Aplastic anemia (AA) is a rare disorder characterized by suppression of bone marrow function. It can develop as the result of congenital marrow disease and chemical exposure; however, most cases are idiopathic. Treatment with immunosuppressive therapy (IST) for patients who do not have an human leukocyte antigen (HLA)-compatible donor relies on the evidence that a deregulated immune system drives T lymphocytes to cytokine-mediated destruction of their own hematopoietic stem cells. The majority of these patients respond well to up-front administration of IST, including anti-thymocyte globulin (ATG) and cyclosporine (CsA), which is successful in around 80%. Unfortunately, ATG and CsA can lead to clonal disorders, in particular myelodysplastic syndrome (MDS) and paroxysmal nocturnal hemoglobinuria. On the other hand, high doses of cyclophosphamide (HDCY) have been administered as a sole immunosuppressive agent in severe aplastic anemia (SAA), principally in adults, with no late clonal disorders reported after up to ten years of follow up. However, late complications following HDCY, including lasting neutropenia and severe fungal infections have been reported mainly in adults, but no similar late complications have been reported for patients who received HDCY during childhood.

We report the first case of a boy with SAA treated successfully with HDCY who after 15 years developed MDS that rapidly evolved into acute myeloid leukemia (AML), and who was treated unsuccessfully with a hematopoietic stem cell transplant (HSCT).

Case report

A five-year-old boy was diagnosed in 1997 with SAA after a short clinical period of fatigue, anemic syndrome and mucocutaneous bleeding, and findings consistent with SAA in his complete blood count (Table 1). Bone marrow aspirate (BMA) and biopsy examinations showed a hypoplastic specimen...
Table 1 – Complete blood count at diagnosis, during myelodysplasia and after progression to acute myeloid leukemia (AML) of a severe aplastic anemia patient treated with high-dose cyclophosphamide who suffered late clonal evolution after 15 years of follow-up.

<table>
<thead>
<tr>
<th></th>
<th>SAA</th>
<th>MDS</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>4.00</td>
<td>7.4</td>
<td>4.88</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>31.9</td>
<td>20.8</td>
<td>14.5</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>101</td>
<td>84.6</td>
<td>84.5</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>16.2</td>
<td>13.5</td>
<td>11.4</td>
</tr>
<tr>
<td>Platelet count (×10^9/L)</td>
<td>15.0</td>
<td>22.4</td>
<td>6.36</td>
</tr>
<tr>
<td>WBC (×10^9/L)</td>
<td>1.52</td>
<td>2.12</td>
<td>5.47a</td>
</tr>
<tr>
<td>Neutrophils (×10^9/L)</td>
<td>0.36</td>
<td>0.45</td>
<td>0.361</td>
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<tr>
<td>Neutrophils (%)</td>
<td>23.7</td>
<td>21.24</td>
<td>6.60</td>
</tr>
<tr>
<td>Lymphocytes (×10^9/L)</td>
<td>1.05</td>
<td>1.4</td>
<td>1.39</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>69.3</td>
<td>66.01</td>
<td>25.4</td>
</tr>
</tbody>
</table>

SAA: severe aplastic anemia; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; MCV: mean corpuscular volume; RDW: red cell distribution width; WBC: white blood cell count.
a 96% myeloid blasts.

Discussion

The treatment of choice for SAA patients who have a matched sibling donor is HSCT with survival rates of up to 90%.1 Front-line matched unrelated donor appears to be a viable option in children, with similar overall survival and event-free survival to transplants with matched sibling donors. A matched unrelated donor HSCT after failure of IST has proved to be a very good rescue strategy.7 As in our case, most SAA patients lack a suitable donor and, in the absence of IST, mortality is 75%.5 Currently, a response rate of 44–80% with a three- to five-year survival rate ranging from 81 to 93% for SAA patients immunosuppressed with ATG plus CsA and granulocyte-colony stimulating factor (G-CSF) has been reported.7 AA patients, however, can have a partial response, fail to respond, relapse, or remain dependent of CsA. In order to circumvent these shortcomings, alternative IST, such as alemtuzumab, as well as promising agents, including eltrombopag, are currently being investigated.

Successful immunosuppressive treatment of SAA with ATG and CsA has been associated with late clonal disorders, including paroxysmal nocturnal hemoglobinuria and MDS.3 High dose cyclophosphamide has also been successfully administered in SAA, mostly in adults, with no such late clonal disorders reported after a decade of follow up.4 There is however, evidence for late complications following HDCY, including lasting neutropenia and severe fungal infections.4 These adverse long-term events have not been reported for patients who received HDCY during childhood. A recent study focusing on the outcomes of pediatric patients with AA found clonal evolution and disease progression to MDS in five patients out of 149 (3%) that had moderate AA.5 Our patient had a stable course with good quality of life for 15 years after successful treatment with HDCY; he then evolved to severe MDS shortly followed by AML, treated unsuccessfully with chemotherapy and followed by a matched related donor HSCT that was complicated by sepsis leading to death.

In conclusion, HDCY for children with SAA who do not have a suitable hematopoietic stem cell donor and no access to standard therapy with ATG plus CsA can lead to long-term hematopoietic regeneration. However, as this case exemplifies for the first time in this age group, late clonal evolution employing high doses of this powerful immunosuppressant agent can lead to MDS and AML.
Acknowledgement

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REFERENCES