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to the editor:

Bridging to transplant with azacitidine in juvenile myelomonocytic leukemia: a retrospective analysis of the EWOG-MDS study group

DNA methyltransferase-inhibiting azanucleosides have become a mainstay of treatment of myeloid neoplasms in adult patients, with 5-azacytidine (azacitidine) being the agent in broadest clinical use. Although not curative, treatment with azacitidine achieves hematologic improvement and transfusion independency in many patients and prolongs survival. Even though most children with juvenile myelomonocytic leukemia (JMML) qualify for allogeneic hematopoietic stem cell transplantation (HSCT), the acceptable toxicity of low-dose azacitidine and its cytoreductive potential make it an attractive option as a bridging therapy before HSCT or as palliation after 1 or more transplants have failed. We previously published the first case report of a boy with JMML who achieved a complete clinical and genetic remission after 8 cycles of azacitidine. Here, we present a retrospective compilation of 12 children with JMML who received individual off-label treatment with azacitidine before HSCT (N = 9) or for relapsed disease (N = 3).

The children were treated at 11 centers November 2007-April 2012. Ten children were enrolled in the studies “98” or “2006” of the European Working Group of Myelodysplastic Syndromes in Childhood (EWOG-MDS; registered at www.clinicaltrials.gov as NCT00047268 and NCT00662090). Approval was obtained from the institutional review board of each institution, and parental informed consent was provided according to the Declaration of Helsinki. Two children were treated at centers not participating in EWOG-MDS studies. One case (D644) was published previously. The diagnosis of all children was centrally reviewed, and response was evaluated according to international consensus criteria.

The median age of the 12 patients was 4.8 years (range 0.4-9.1) (Table 1). A total of 64 azacitidine cycles were administered (median 5.5 cycles, range 1-11). Seven of 12 treatments consisted of 100 mg/m² azacitidine per intravenous infusion on 5 consecutive days every 28 days. In the other 5 patients, the substance was administered over 5 to 7 days at a single dose of 50 to 100 mg/m² per intravenous or subcutaneous route every 28 to 42 days.

Severe neutropenia (≤500/µL) was observed in 4 children. Cytopenias led to dose reduction in 2 children, both treated for relapse after second HSCT. Other adverse events were gastrointestinal problems including nausea and vomiting in 2 children, skin rash in 2 children, and fatigue or slight creatinine elevation in 1 patient each. Seven episodes of infection were reported for a total of 64 azacitidine cycles (10.9%).

Of 9 children treated prior to HSCT, 3 normalized blood counts and spleen size (scored as clinical CR) (Table 1). In 2 of these patients, monosomy 7 was present in leukemic cells but disappeared after cycles 5 and 6, respectively. The leukemic karyotype was normal in the other child with clinical CR, precluding the assessment of cytogenetic response. Two of the 3 CR patients featured a somatic mutation. The mutation became undetectable after cycles 5 and 6, respectively. The leukemic karyotype was normal in the other child with clinical CR, precluding the assessment of cytogenetic response. Two of the 3 CR patients featured a somatic PTPN11 gene mutation. The mutation became undetectable after cycle 6 in 1 child (NS002); material for mutational analysis under azacitidine was unavailable from the other child (D827). The third child (CH058) experienced considerable regression of spleen size and became transfusion independent (scored as clinical PR). All 4 children underwent HSCT after 7 to 11 cycles. A fifth child (NS001) responded unusually early, as indicated by reduction of splenomegaly after the first cycle and hematologic improvement after cycle 3 (scored as clinical PR). Azacitidine was then discontinued because of parental choice. Three children progressed rapidly under azacitidine and underwent expedited HSCT. One child (I255) was not evaluable for response because of concomitant treatment. Three children with JMML received azacitidine for leukemia recurrence after the second HSCT. They achieved clinical PR or could be maintained in stable disease for 4 cycles before progressing.
In summary, this retrospective series indicates that low-dose azacitidine is effective and tolerable in JMML and documents 3 cases of JMML where azacitidine induced complete clinical, cytogenetic, and/or molecular genetic remissions before allogeneic HSCT. Importantly, complete remissions without HSCT have not been documented for JMML thus far, regardless of whether conventional cytostatic chemotherapy or newer experimental agents were applied.7-10

Prospective clinical investigation of azacitidine, such as the ongoing collaborative Innovative Therapies in Childhood Cancer/EWOG-MDS phase 1/2 trial (Eudra-CT 2010-022235-10), is needed to clarify these questions.

### Table 1. Response to azacitidine in children with JMML

<table>
<thead>
<tr>
<th>Disease status</th>
<th>Patient identifier</th>
<th>Age (y) and gender</th>
<th>Cytogenetics</th>
<th>Mutational group*</th>
<th>Azacitidine cycles</th>
<th>Concomitant treatment</th>
<th>Response to azacitidine†</th>
<th>HSCT (total number)</th>
<th>Status</th>
<th>Follow-up (mo)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to first HSCT</td>
<td>A062</td>
<td>1.1, male</td>
<td>Del(5)(q13q33)</td>
<td>NRAS</td>
<td>1</td>
<td>None</td>
<td>PR</td>
<td>Yes (2)</td>
<td>Alive with leukemia</td>
<td>38</td>
</tr>
<tr>
<td>Prior to first HSCT</td>
<td>CH058</td>
<td>2.8, male</td>
<td>Normal</td>
<td>PTPN11</td>
<td>1-3</td>
<td>None</td>
<td>SD</td>
<td>Yes (2)</td>
<td>Alive with leukemia</td>
<td>16</td>
</tr>
<tr>
<td>Prior to first HSCT</td>
<td>D644‡</td>
<td>1.4, male</td>
<td>−7</td>
<td>KRAS</td>
<td>1</td>
<td>None</td>
<td>PD</td>
<td>Yes (1)</td>
<td>Alive in remission</td>
<td>62</td>
</tr>
<tr>
<td>Prior to first HSCT</td>
<td>D706</td>
<td>5.9, male</td>
<td>−7</td>
<td>PTPN11</td>
<td>1</td>
<td>None</td>
<td>PD</td>
<td>Yes (3)</td>
<td>Alive in remission</td>
<td>66</td>
</tr>
<tr>
<td>Prior to first HSCT</td>
<td>D712</td>
<td>6.3, female</td>
<td>Normal</td>
<td>NRAS</td>
<td>1</td>
<td>None</td>
<td>PD</td>
<td>Yes (1)</td>
<td>Dead, TRM</td>
<td>1</td>
</tr>
<tr>
<td>Prior to first HSCT</td>
<td>D827</td>
<td>0.4, male</td>
<td>Normal</td>
<td>PTPN11</td>
<td>1-2</td>
<td>6MP</td>
<td>Not evaluable</td>
<td>Yes (1)</td>
<td>Alive in remission</td>
<td>38</td>
</tr>
<tr>
<td>Prior to first HSCT</td>
<td>I255</td>
<td>9.1, male</td>
<td>Inv(2)(p23q13), −7</td>
<td>No mutation</td>
<td>1-4</td>
<td>AraC, 6MP</td>
<td>Not evaluable</td>
<td>Yes (1)</td>
<td>Alive in remission</td>
<td>49</td>
</tr>
<tr>
<td>Prior to first HSCT</td>
<td>NS001</td>
<td>5.4, male</td>
<td>−7</td>
<td>NRAS</td>
<td>1-3</td>
<td>None</td>
<td>PR</td>
<td>No</td>
<td>Dead, progressive disease</td>
<td>No data</td>
</tr>
<tr>
<td>Prior to first HSCT</td>
<td>NS002</td>
<td>0.8, male</td>
<td>−7</td>
<td>PTPN11</td>
<td>1</td>
<td>2-3</td>
<td>None</td>
<td>SD</td>
<td>Yes (1)</td>
<td>Dead, TRM</td>
</tr>
<tr>
<td>Relapse after HSCT*</td>
<td>NL121</td>
<td>4.6, male</td>
<td>Not done</td>
<td>PTPN11</td>
<td>2-4</td>
<td>None</td>
<td>SD</td>
<td>Yes (3)</td>
<td>Dead, third relapse</td>
<td>6</td>
</tr>
<tr>
<td>Relapse after HSCT**</td>
<td>SC108</td>
<td>5.0, male</td>
<td>Normal††</td>
<td>NF1</td>
<td>1-2</td>
<td>None</td>
<td>SD</td>
<td>Yes (2)</td>
<td>Dead, progressive disease</td>
<td>1</td>
</tr>
<tr>
<td>Relapse after HSCT**</td>
<td>SC156</td>
<td>5.3, male</td>
<td>Normal††</td>
<td>PTPN11</td>
<td>2-4</td>
<td>None</td>
<td>PD</td>
<td>Yes (3)</td>
<td>Dead, third relapse</td>
<td>5</td>
</tr>
</tbody>
</table>

| ArA, cytarabine; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; 6MP, 6-mercaptopurine; TRM, transplantation-related mortality. |
| *All mutations were confirmed to be somatic. Neurofibromatosis type 1 was diagnosed clinically. |
| †Cycles of azacitidine with concomitant antineoplastic medication were considered not evaluable. |
| ‡This case was published previously by Furlan et al. § |
| ††Last cytogenetic analysis: SC108, at start of azacitidine treatment; SC156, prior to second HSCT. |
| **Relapse after second HSCT. |
| ††Last cytogenetic analysis: SC108, at start of azacitidine treatment; SC156, prior to second HSCT. |

### Authors

Ayami Yoshimi  
Division of Pediatric Hematology-Oncology, Department of Pediatrics and Adolescent Medicine, University Medical Center, Freiburg, Germany

Michael Dworzak  
St. Anna Children’s Hospital and Children’s Cancer Research Institute, Department of Pediatrics, Medical University of Vienna, Vienna, Austria

Henrik Hasle  
Department of Pediatrics, Aarhus University Hospital, Skejby, Denmark

Franco Locatelli  
Department of Pediatric Hematology-Oncology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ospedale Bambino Gesù, Rome, Italy

Riccardo Masetti  
Pediatric Oncology and Hematology, University of Bologna, Bologna, Italy

Annamaria Cseh  
Division of Pediatric Hematology-Oncology, Department of Pediatrics and Adolescent Medicine, University Medical Center, Freiburg, Germany

Charlotte M. Niemeyer  
Division of Pediatric Hematology-Oncology, Department of Pediatrics and Adolescent Medicine, University Medical Center, Freiburg, Germany

German Cancer Consortium (DKTK), Heidelberg, Germany

Riccardo Masetti  
Pediatric Oncology and Hematology, University of Bologna, Bologna, Italy
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Correspondence: C. Flotho, Division of Pediatric Hematology-Oncology, Department of Pediatrics and Adolescent Medicine, University Medical Center, Mathildenstrasse 1, 79106 Freiburg, Germany; e-mail: christian.flotho@uniklinik-freiburg.de.

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