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Efficacy of prolonged therapy with combined arsenic trioxide and ATRA for relapse of acute promyelocytic leukemia

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Front-line treatment combining All-trans retinoic acid (ATRA) and chemotherapy is curative in approximately 80% of patients with acute promyelocytic leukemia (APL). As for patients who relapse after this approach, current guidelines recommend the administration of arsenic trioxide (ATO) with or without ATRA. Given its high efficacy in inducing durable molecular remission (CRm), ATO is considered the most active single agent in APL and is currently being also investigated in various combinations as front-line therapy. While the role of ATO in remission re-induction is well established, the best consolidation strategy to be used in relapsed APL still remains controversial. In fact, because of the few patient numbers involved, no randomised studies are available which may definitely support a given consolidation (allo-HSCT, auto-SCT, further ATO or chemotherapy). This notwithstanding, most investigators would nowadays recommend to proceed to HSCT after re-induction of CRm. However, the effect of prolonged ATO administration beyond consolidation, particularly for patients unfit to receive HSCT or as an alternative to the latter for patients with better prognosis (e.g. long duration of 1st CR) has not been widely investigated. We report here on the outcome of 9 patients with relapsed APL, who received prolonged therapy with an ATO plus ATRA combination. Nine patients with
relapsed APL were treated with prolonged ATRA and ATO at the Department of Cellular Biotechnologies and Hematology of the University La Sapienza (6 cases) and at the Department of Biopathology of the University Tor Vergata (3 cases) of Rome. The main clinico-biological features and treatment outcome of the 9 patients are shown in Table 1. UPN 5 and UPN 6 have been reported previously. At time of ATO/ATRA initiation, 7 patients were in 1st molecular relapse, whereas UPN 8 and 9 were in 2nd haematological and 2nd molecular relapse, respectively. The median time of molecular or hematologic 1st CR duration was 1.9 years (range 1-7). All patients received ATO/ATRA according to the schedule reported by Estey et al for a total of 5 ATO and 8 ATRA courses given at monthly and bi-weekly intervals, respectively. Patients in this series were kept on such prolonged therapy and not offered an HSCT option because of long 1st CR duration (3 cases), HSCT refusal (3 cases), age (3 cases). Complete molecular response as assessed by nested RT-PCR of PML/RARA was achieved in all patients after 1 (2 cases) or 2 cycles (7 cases). Two patients experienced mild toxicity during re-induction therapy consisting of transient QTc prolongation and grade 2 neutropenia, respectively, requiring temporary ATO discontinuation. Another patient treated for molecular relapse experienced electrolyte abnormalities with no QTc prolongation which was corrected by electrolyte replacement and did not require discontinuation of the drug. Only two patients required hospitalization because they were treated for hematologic relapse (for a total of 30 days), while all the others were treated as outpatients during induction, consolidation and maintenance treatment. Of the 9 patients, 8 remained in prolonged 2nd CRm for a median time of 25 mos. (range 11-50) and 1 (UPN1) underwent 2nd molecular relapse during PCR monitoring at 10 months after initiation of ATO-based salvage therapy (Table 1). The latter patient received allogeneic HSCT and is currently in 3rd CR. Though limited to a small number of patients, our observation suggests that prolonged ATO/ATRA without HSCT represents a valid and potentially curative therapeutic option for relapsed APL. Based on the characteristics of our series, this assumption might particularly apply to patients who are treated with this regimen for late relapse. This parameter, together with patient decision of HSCT refusal and advanced age in some cases, was the driven criterion for assessing the efficacy of the prolonged ATO/ATRA combination in relapsed APL. The French group reported a randomized study on 20 relapsed APL patients who received ATO alone or in combination with ATRA, showing that 80% of patients achieved hematologic CR after one cycle. On the other hand, a recent update of the Estey study who first reported this regimen in newly diagnosed patients, demonstrated considerable
efficacy with excellent outcome in particular for non-high risk APL\textsuperscript{7}. As an additional cautionary criterion, all patients in the present series were closely monitored by Rt-PCR in order to allow pre-emptive therapeutic intervention and the use of HSCT in case of a further molecular relapse. Of note, previously reported UPN 6 delivered a healthy baby after ATO/ ATRA salvage \textsuperscript{5}, and her 2\textsuperscript{nd} CR currently exceeds already the duration of 1st CR induced by ATRA and chemotherapy. Our results are comparable to those obtained in a recently reported series of 13 patients who received autologous HSCT in 2\textsuperscript{nd} molecular CR. Relapses were in that study hematological in 12 cases and molecular in 1 case. All patients were treated with chemotherapy and after consolidation all achieved CRm: 10/13 patients (77\%) were alive and well after a median follow-up of 25 months from 2nd CR\textsuperscript{8}. We report here similar results with an ATO-based salvage therapy, with 88\% of patients remaining in prolonged CRm without transplant procedures. Further studies in larger series are warranted to better establish whether autologous and allogeneic HSCT might be avoided in patients with late relapse APL receiving a prolonged ATO plus ATRA therapy.
References


Table 1. Clinical and biological features of patients treated with ATO+ATRA for relapsed APL.

<table>
<thead>
<tr>
<th>UPN</th>
<th>Sex/age*</th>
<th>FAB</th>
<th>WBC (x 10^9/l)</th>
<th>Relapse risk</th>
<th>Previous treatments</th>
<th>Duration of previous CR(s)</th>
<th>Disease status at time of ATO+ATRA Initiation</th>
<th>Toxicity during ATO + ATRA</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/51</td>
<td>M3</td>
<td>2.5</td>
<td>Low</td>
<td>AIDA§</td>
<td>15 months</td>
<td>1st molecular relapse</td>
<td>no</td>
<td>relapsed at 10 mos</td>
</tr>
<tr>
<td>2</td>
<td>M/54</td>
<td>M3</td>
<td>3.5</td>
<td>Interm</td>
<td>AIDA</td>
<td>12 months</td>
<td>1st molecular relapse</td>
<td>QTc prolongation</td>
<td>CRm^ (22+ mos)</td>
</tr>
<tr>
<td>3</td>
<td>F/46</td>
<td>M3</td>
<td>4.2</td>
<td>Interm</td>
<td>AIDA</td>
<td>32 months</td>
<td>1st molecular relapse</td>
<td>no</td>
<td>CRm (28+ mos)</td>
</tr>
<tr>
<td>4</td>
<td>F/70</td>
<td>M3</td>
<td>5.1</td>
<td>Interm</td>
<td>AIDA</td>
<td>28 months</td>
<td>1st molecular relapse</td>
<td>no</td>
<td>CRm (18+ mos)</td>
</tr>
<tr>
<td>5</td>
<td>M/38</td>
<td>M3</td>
<td>1.0</td>
<td>Interm</td>
<td>AIDA</td>
<td>84 months</td>
<td>1st EM° and molecular relapse</td>
<td>no</td>
<td>CRm (39+ mos)</td>
</tr>
<tr>
<td>6</td>
<td>F/32</td>
<td>M3</td>
<td>4.2</td>
<td>Interm</td>
<td>AIDA</td>
<td>48 months</td>
<td>1st molecular relapse</td>
<td>no</td>
<td>CRm (50+ mos)</td>
</tr>
<tr>
<td>7</td>
<td>M/61</td>
<td>M3v</td>
<td>9.5</td>
<td>Interm</td>
<td>AIDA</td>
<td>17 months</td>
<td>1st molecular relapse</td>
<td>Electrolyte abnormalities</td>
<td>CRm (14+ mos)</td>
</tr>
<tr>
<td>8</td>
<td>M/69</td>
<td>M3</td>
<td>1.8</td>
<td>Low∞</td>
<td>AIDA / GO# + ATRA</td>
<td>22 months /12 months</td>
<td>2nd hematologic relapse</td>
<td>no</td>
<td>CRm (31+ mos)</td>
</tr>
<tr>
<td>9</td>
<td>M/52</td>
<td>M3</td>
<td>11</td>
<td>High</td>
<td>AIDA / ARA-C + MTZ@</td>
<td>17 months /13 months</td>
<td>2nd molecular relapse</td>
<td>neutropenia (grade 2)</td>
<td>CRm(11+ mos)</td>
</tr>
</tbody>
</table>

*Age at time of ATRA+ATO initiation. §AIDA protocol including idarubicin and ATRA; ^CRm, molecular remission: 
°extramedullary; # gemtuzumab ozogamicin; CRm: complete molecular remission; @MTZ: mitoxantrone. 
∞Relapse risk at relapse high. NA° Not available