



## Arsenic trioxide in the treatment of acute promyelocytic leukemia. A review of current evidence

Miguel A. Sanz  
Pierre Fenaux  
Francesco Lo Coco  
on behalf of the European  
APL Group of Experts

Recent studies have demonstrated the beneficial effects of arsenic trioxide (ATO) in the treatment of relapsed acute promyelocytic leukemia (APL). The aim of this review is to discuss the role of ATO in the management of APL. Based on the available clinical evidence, a tentative algorithm is proposed for the treatment of patients who relapse after or are refractory to all trans-retinoic acid-based therapy. Other opportunities for the use of ATO in front-line treatment of APL are also discussed, especially its potential use in patients at high risk of relapse and in those with contraindications to chemotherapy or in whom the amount of chemotherapy should be reduced.

Key words: arsenic trioxide, acute promyelocytic leukemia.

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From the University Tor Vergata, Rome (SA); Universitäts Klinikum Munster, Munster (TB); University of Wales College of Medicine, Cardiff (AKB); University "La Sapienza", Rome (GC); Universitätsklinikum Ulm, Ulm (HD); Institut Universit  d'Hematologie Hopital St. Louis, Paris (HD); Universit ts Klinikum Mannheim, Mannheim (EL); University Tor Vergata, Rome (FLC); Erasmus University Hospital Rotterdam-Dijkzigt, Rotterdam (BL); Wilhelminenspital, Vienna (HL); Universit  Paris 13, Bobigny, Paris (PF); Hospital Universitario La Fe, Valencia (MS).

Correspondence:  
Miguel A. Sanz, Servicio de Hematolog a, Hospital Universitario La Fe, Avenida Campanar 21, 46009 Valencia, Spain.  
E-mail: msanz@uv.es

In the early 1990s, treatment protocols for newly diagnosed acute promyelocytic leukemia (APL) were revolutionized by the introduction of all-trans retinoic acid (ATRA) treatment. ATRA combined with anthracycline-based chemotherapy and followed by maintenance treatment combining intermittent ATRA and continuous low dose chemotherapy, improved the cure rate in patients with newly diagnosed APL to 70%, up from 35% in patients treated with chemotherapy alone.<sup>1,2</sup> Nevertheless, about 20% of patients who attain a complete remission will eventually relapse.<sup>3-8</sup>

Treatment approaches for relapsed patients have been quite variable. Initial findings reported from China and more recent studies from the USA demonstrate the beneficial effects of arsenic trioxide (ATO) in the treatment of relapsed APL.<sup>9-14</sup> The aim of this review is to discuss the role of ATO in the management of APL in view of the available clinical evidence.

### Arsenic trioxide

ATO is an active drug in refractory/relapsed APL and has at least two antileukemic mechanisms of action.<sup>9,15,16</sup> First, ATO degrades PML RAR $\alpha$ , the fusion protein of the APL gene, thereby removing the negative inhibition of retinoid signal transduction and allowing for partial differentiation of the abnormal APL promyelocytes. Second, ATO induces

apoptosis in APL cells. ATO monotherapy in patients with relapsed APL resulted in remission rates of more than 80%, which was accompanied by molecular remissions (i.e. conversion to polymerase chain reaction [PCR] negative status for PML/RAR $\alpha$  in the marrow) after two cycles in the majority of cases.<sup>9-14</sup> Use of ATO prior to stem cell transplant resulted in an estimated 3-year survival rate of 78%. In the USA multicenter trial,<sup>13</sup> conversion to reverse-transcriptase PCR negativity, using a low-sensitivity method, occurred in 48% after induction with ATO alone and in 86% of patients after a subsequent consolidation course with this agent. These results confirm ATO as the most efficient single anti-APL agent. The number of ATO cycles required for the optimum molecular remission rate is still unclear, but at least two cycles are recommended. In contrast to conventional antibody-conjugated chemotherapy, ATO treatment does not induce severe myelosuppression.

Although most patients treated with ATO experience some toxicity, ATO is generally well tolerated and its tolerable profile compares favorably with that of intensive salvage chemotherapy. The significant adverse effects (APL differentiation syndrome, hyperleukocytosis, prolongation of QT/QTc interval and renal or hepatic impairment) are few and manageable.<sup>9-14,17</sup> However, other non-life-threatening adverse events are also commonly

observed in patients receiving ATO therapy, such as nausea and vomiting, cough, fatigue, headache, insomnia, diarrhea, tachycardia, hypokalemia and hyperglycemia. Although severe neuropathy has been rarely observed, mild peripheral neuropathy, which usually resolves after ATO discontinuation, has been reported in approximately 40% of patients.<sup>13</sup> In addition to careful monitoring of the QT interval, it is recommended that serum potassium and magnesium levels are maintained above 4.0 mmol/L (4.0 mEq/L) and 0.82 mmol/L (2.0 mg/dL), respectively.

**Diagnosing relapse**

Molecular remission is a mandatory therapeutic objective in APL, as was recently established by an international expert panel.<sup>18</sup>

Molecular monitoring of minimal residual disease by qualitative nested reverse transcriptase-PCR and quantitative real-time PCR of PML/RAR $\alpha$  allows the identification of molecular persistence or relapse, which is generally followed by hematologic relapse within 2 to 20 weeks in the absence of therapeutic intervention.<sup>19</sup> Although the clinical advantage of using quantitative real time-PCR remains to be determined in longitudinal prospective studies, it is conceivable that, if appropriate cut-offs are defined, real-time assays may become more useful in the future. So far, the predictive value has only been demonstrated in studies in which low-sensitivity amplification techniques (with sensitivity thresholds comprised between 10<sup>-3</sup> and 10<sup>-4</sup>) were used.<sup>19</sup>

A pilot study conducted in Italy suggested that early therapeutic intervention at the time of molecular relapse provides a survival advantage over treating hematologic disease recurrence.<sup>20</sup> These results were confirmed in an extended Italian series and by the Spanish PETHEMA group.<sup>21,22</sup> As an effective inducer of molecular remission, ATO might be used alone or in combination with other agents to treat molecular relapse in APL, although no experience has been reported to date in this context.

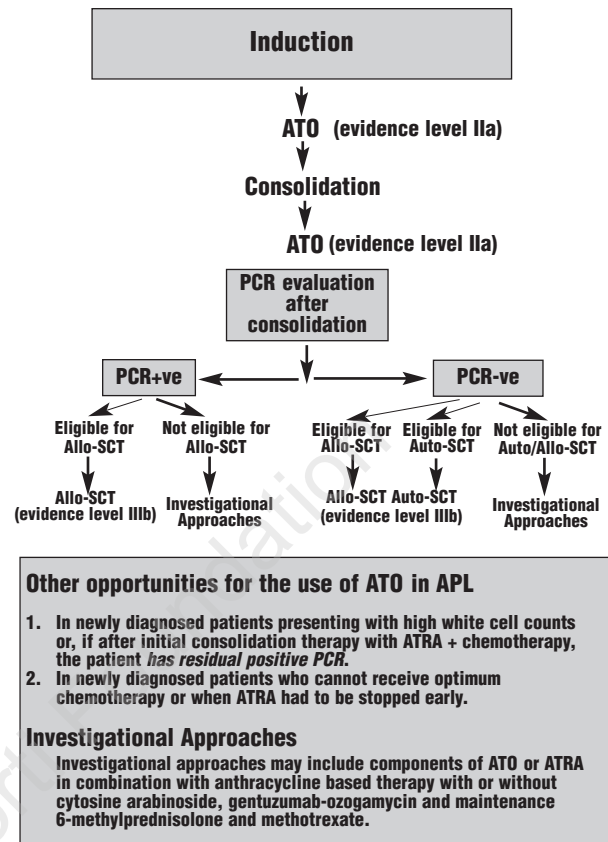
**The place of ATO in relapsed/refractory patients**

A possible algorithm for the treatment of relapsed or refractory patients is shown in Figure 1 and Table 2. Definitions of the levels of the evidence and grades of the recommendations are summarized in Table 1.

**Induction**

Patients experiencing early relapse (i.e. within 6 months after the first complete remission) or relapse while on ATRA maintenance therapy are very unlikely to respond to further ATRA treatment.<sup>23</sup> Therefore, these patients may be given ATO at a

**Figure 1.** Treatment algorithm for patients with relapsed or refractory APL.



dose of 0.15 mg/kg/day intravenously until the marrow is cleared of blasts (maximum 50 days) [level of evidence IIa].<sup>9-14</sup> One possible side-effect of ATO is the differentiation syndrome (similar to that observed with ATRA), which is usually preceded or accompanied by leukocytosis.<sup>17</sup> The APL differentiation syndrome requires prompt addition of high dose steroids and, in the view of many authors, conventional chemotherapy to reduce the white cell count. For patients who relapse after discontinuation of ATRA, the use of ATO is also an attractive possibility, even though a further induction course of ATRA and chemotherapy may be an alternative. The disadvantage of the use of ATRA combined with chemotherapy is that it may result in severe myelosuppression. Antibody-conjugated treatments, such as gentuzumab-ozogamicin, are currently under investigation in relapsing APL.<sup>24</sup>

**Consolidation**

Whatever treatment is chosen to re-induce remission, further consolidation with autologous or allogeneic stem cell transplantation is usually recom-

**Table 1.** Definitions of the levels of the evidence and grades of the recommendations used in the algorithm.

Level of evidence		
Level	Type of evidence	
Ia	Evidence obtained from meta-analysis of randomized controlled trials	
Ib	Evidence obtained from at least one randomized controlled trial	
IIa	Evidence obtained from at least one well-designed controlled study without randomization	
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study	
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies	
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities	

Grade of recommendation		
Grade	Evidence level	Recommendation
A	Ia, Ib	Required - at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation
B	IIa, IIb, III	Required - availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C	IV	Required - evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
D		Indicates absence of directly applicable clinical studies of good quality

**Table 2.** Treatment options for relapsed/refractory APL.

<b>Induction</b>
ATO (0.15 mg/kg/day, until complete remission or 50 days)
<b>Consolidation</b>
1 <sup>st</sup> course: ATO (0.15 mg/kg/day, on days 1-5 for 5 weeks)
2 <sup>nd</sup> course: ATO (0.15 mg/kg/day, on days 1-5 for 5 weeks)
<b>After Consolidation</b>
If PCR negative and eligible for transplantation: autologous or allogeneic stem cell transplantation should be offered
If PCR negative and not eligible for transplantation: ATO + ATRA should be offered as an investigational therapy
If PCR positive with family or unrelated donor available: allogeneic stem cell transplantation should be offered
If PCR positive but with no donor available or with contraindications to stem cell transplantation: post-consolidation ATO ± ATRA could be offered

mended to obtain sustained response [level of evidence IIb].<sup>1,2,24,25</sup> Autologous stem cell transplantation in patients with molecularly positive APL is usually associated with relapse. Therefore, patients who do not achieve molecular remission after re-induction should be considered for allogeneic stem cell transplantation, if practically and medically feasible. In

contrast, patients in molecular relapse who convert to molecular remission have a low risk of subsequent relapse following autologous stem cell transplantation [level of evidence IIb].<sup>25-27</sup> The overall outcome is similar to that achieved by allogeneic stem cell transplantation and may therefore be preferable for the PCR negative patient who has a PCR negative donation available.

At least two, and sometimes three cycles of ATO (i.e. at least one induction course and one or two consolidation courses, 5 days x 5 weeks) are required to achieve molecular remission [level of evidence: IIa]<sup>9-14</sup> Patients remaining PCR positive after three courses of ATO should be considered as having failed to respond and should be offered alternative treatments. Therefore, PCR evaluation of minimal residual disease appears to be crucial in the therapeutic decision process. The value of PCR analysis depends on the sensitivity of the test used. Low-sensitivity tests with detection thresholds of  $10^{-3}/10^{-4}$  have proven more informative from a clinical viewpoint than have assays of higher sensitivity.<sup>21</sup> In the case of PCR positivity (with proven predictive value for relapse) and the availability of a suitable donor, allogeneic stem cell transplantation is recommended.<sup>25,28</sup> If no donor is available or in the case of medical contraindications to allogeneic stem cell transplantation every effort should be made to reach PCR negativity, using any of the variety of possible combinations of ATRA, ATO, anthracyclines with or without Ara-C, gentuzumab-ozogamycin and maintenance with 6-mercaptopurine and methotrexate, which has a demonstrated effect on APL cells. If the patient becomes PCR negative, either autologous or allogeneic stem cell transplantation should be offered [level of evidence: III]. The European Bone Marrow Transplantation Cooperative Group and The European APL Group found a lower relapse rate with allogeneic stem cell transplantation but this was associated with a higher treatment-related mortality (although not in the context of ATO prescribing or PCR information).<sup>29</sup> Due to its ability to induce molecular remission and in light of its limited myelosuppression and other toxicities, ATO functions as a suitable *bridge* to stem cell transplantation in APL.<sup>30,31</sup>

#### Other opportunities for the use of ATO in APL

There is increasing evidence suggesting that ATO may be used in the front-line treatment of APL. In this situation, ATO can be used during induction and/or consolidation treatment. A recent Chinese study provided strong evidence of a synergistic effect between ATO and ATRA in rapidly reducing PML-RAR $\alpha$  transcripts during induction therapy of APL.<sup>32</sup> Preliminary results of other studies also suggest that ATO, with or without ATRA, can yield complete

remission rates of about 90% in newly diagnosed APL.<sup>33,34</sup> On the other hand, several of those reports suggest that the use of ATO (with or without ATRA) during induction treatment of newly diagnosed APL may be associated with a relatively high incidence of severe leukocyte activation syndrome which, in the series of Ghavamzadeh *et al.*,<sup>34</sup> was responsible for four early deaths in 66 treated patients. Whether this problem can be mitigated by early addition of chemotherapy (as is the case for leukocyte activation syndrome due to ATRA alone) remains to be demonstrated.

Therefore, most clinicians, at least in countries in which ATRA anthracycline-based chemotherapy and intensive supportive care are financially acceptable strategies, currently prefer to test ATO during consolidation treatment, mainly in two types of situations: (i) *in newly diagnosed APL patients at high risk of relapse*; patients at high risk of relapse include patients presenting with white cell counts greater than  $10 \times 10^9/L$  and those with persistent PCR positivity after consolidation.<sup>3-8</sup> Current front-line therapy for patients with elevated white cell counts involves ATRA plus anthracycline-based chemotherapy, with or without cytosine arabinoside, and maintenance treatment with intermittent ATRA and low dose chemotherapy. Used for consolidation, in addition to current consolidation and maintenance regimens, ATO may reduce the incidence of relapse in those patients (level of evidence: IV). This aspect is currently under investigation in the USA and Europe; the results of a USA Intergroup trial which recently closed inclusion are particularly awaited. The small fraction of patients who remain PCR positive following induction and consolidation with ATRA plus chemotherapy may also be candidates for ATO-based treatment before maintenance therapy is started;<sup>5,35</sup> (ii) *in newly diagnosed patients with contraindications to chemotherapy or in patients in whom the amounts of chemotherapy should be limited*; this group includes elderly patients and possibly children, in whom the use of cumulative anthracycline doses administered in current APL trials is of concern. The toxicity of intensive chemotherapy is often unacceptable in patients of older age in whom toxic deaths in complete remission are generally due to myelosuppression (ranging from 10 to 20%).<sup>3-8</sup> As recently shown by the GIMEMA group, reducing the number of chemotherapy consolidation cycles in older patients does not increase the incidence of relapse.<sup>36</sup> Furthermore, the PETHEMA group reported a high antileukemic effi-

cacy combined with very low toxicity and high compliance to treatment using anthracycline-based chemotherapy (without cytosine arabinoside) plus ATRA in older patients with APL.<sup>37</sup> However, adding ATO, a non-myelosuppressive drug, to the consolidation regimen, may allow for further reduction of the dose-intensity of chemotherapy. This deserves further study.

The front-line use of ATO in children may, however, be slowed by concerns over potential very long-term side effects.

## Conclusions

Use of ATO in refractory/relapsed APL results in high complete remission and molecular remission rates associated with lower toxicity compared to chemotherapy combined with ATRA. Therefore, ATO could be considered as the first-choice therapy for induction and consolidation in such patients with the intention of delivering stem cell transplantation. The suitability of ATO as initial treatment of APL in patients at high risk of relapse and in patients in whom the amount of chemotherapy should be limited is currently being investigated

## Appendix

*Members of the European APL Group of Experts in alphabetical order: Sergio Amadori, University Tor Vergata, Rome; T Buchner, Universitäts Klinikum Munster, Munster; Alan K Burnett, University of Wales College of Medicine, Cardiff; Giuseppe Cimino, University "La Sapienza", Rome; H. Doehner, Universitätsklinikum Ulm, Ulm; Hervé Dombret, Institut Université d'Hématologie Hopital St. Louis, Paris; E Lengfelder, Universität Klinikum Mannheim, Mannheim; Francesco Lo Coco, University Tor Vergata, Rome; Bob Lowenberg Erasmus University Hospital Rotterdam-Dijkzigt, Rotterdam; H Ludwig, Wilhelminenspital, Vienna; Pierre Fenaux, Université Paris 13, Bobigny, Paris; Miguel Sanz, Hospital Universitario La Fe, Valencia, Spain.*

*MAS, PF and RLC contributed equally to the writing and conception of this paper that conveys the opinions shared with a European APL group of experts.*

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