Sustained molecular remission in advanced acute promyelocytic leukemia with combined pulsed retinoic acid and arsenic trioxide. Clinical evidence of synergistic effect and real-time quantification of minimal residual disease

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The treatment of acute promyelocytic leukemia (APL) patients who present or develop resistance to ATRA is still a problem. Recently, we proposed a pulsed-ATRA regimen, able to reduce the incidence of resistance if compared to continuous administration, and to re-induce complete molecular remission in relapsed patients. Arsenic trioxide (As$_2$O$_3$) is effective in APL refractory or relapsed after ATRA-based therapies. In vitro data show that As$_2$O$_3$ and ATRA have synergetic effects, inducing apoptosis also in ATRA-resistant APL cell. Moreover, the association of these two drugs has shown good results in vivo. However, up to now, no data are available regarding the restoration of sensitivity to ATRA after As$_2$O$_3$ exposure. Monitoring minimal residual disease with RT-PCR is now considered a mainstay in the management of molecular relapse. The quantification of minimal residual disease by RT-PCR (Taqman$^{	ext{TM}}$) can improve this strategy, identifying early evidence of disease recurrence. We present a case in which sensitivity to ATRA was for the first time restored after As$_2$O$_3$ treatment, providing a quantification of the minimal residual disease. A diagnosis of APL was made in a 50-year old man. He was treated with the AIDA scheme, obtaining a molecular complete remission (mCR). Three years later the patient molecularly relapsed and was then treated with a pulsed-ATRA regimen, obtaining a second mCR. Four months later, he presented with a second molecular relapse, with progressive expansion of the leukemic population while on therapy with ATRA. We thus administered As$_2$O$_3$ (0.15 mg/Kg/day for 28 days) alone. Following this course, we documented an increase of the PML/RARa transcript copies; the cytogenetic analysis became positive (Figure 1). As no HLA compatible donor was available, we decided to re-administer a pulsed ATRA regimen. After 8 weeks of therapy, we documented a new mCR. We then decided to administer 3 other course of As$_2$O$_3$ (0.15 mg/Kg/day for 15 days, every 3 months) with pulsed-ATRA among these cycles, as consolidation. The mCR persists so far, with a follow up of 15 months (Figure 1).

ATRA-based regimens are considered the gold standard therapy for APL. The possible occurrence of ATRA resistance is a problem. Clinical and biological observations have shown that continuous ATRA administration can induce resistance in APL cells. Recent evidence suggests that the failure of APL cells to undergo apoptosis is involved in the pathogenesis of ATRA resistance. It is possible that APL cells resistant to ATRA enhance the expression of anti-apoptotic genes, such as bcl-2. As$_2$O$_3$ can potently downregulate bcl-2 expression at the mRNA and protein levels, and thus can restore susceptibility of cells to undergo apoptosis. Moreover, there is evidence that ATRA can induce the degradation of PML-RARA, probably involving the proteasome system, whereas As$_2$O$_3$ can modulate the PML-RARA/PML ratio. These places of evidence suggest that As$_2$O$_3$ could work through different mechanisms from ATRA, and thus APL cells resistant to ATRA could be sensitive to As$_2$O$_3$. Although until now no demonstration was available that As$_2$O$_3$ restores ATRA sensitivity in vivo, the association between As$_2$O$_3$ and ATRA seems to be more effective than As$_2$O$_3$ alone in ATRA-resistant APL patients.

Based on this, we used As$_2$O$_3$ to treat a 50-year old man with APL in second relapse during ATRA maintenance therapy. Unfortunately, after the first course of As$_2$O$_3$, we observed disease progression by molecular and cytogenetic analysis, and we then re-administered a pulsed-ATRA regimen. The patient re-obtained a mCR after 8 weeks of therapy; after 15 months the patient is still in third mCR. The quantification of minimal residual disease by RT-PCR showed a straight reduction in the amount of PML-RARA fusion gene transcript after pulsed ATRA therapy was restarted (Figure 1). We concomitantly studied the expression of bcl-2 mRNA with RT-PCR before, during and after treatment with As$_2$O$_3$ and ATRA, in order to establish whether a correlation between bcl-2 expression, resistance to ATRA and apoptosis was present. Interestingly, in our case, bcl-2 was over-expressed after As$_2$O$_3$ administration. In our opinion, this phenomenon might explain the clinical resistance to As$_2$O$_3$ in fact, it has been demonstrated in vitro that As$_2$O$_3$ induces apoptosis by bcl-2 downregulation. Probably, in this case, As$_2$O$_3$ modified the gene network of apoptosis, without altering the bcl-2 pattern, giving the opportunity for ATRA to regain efficacy. In our opinion, As$_2$O$_3$ played a significant role in re-inducing the sensitivity to ATRA. In fact, the interval of 3 months between the ATRA courses was probably not sufficient to justify the re-acquired sensitivity to retinoids. In conclusion, we think that sequential administration of As$_2$O$_3$ and pulsed ATRA might be useful in APL patients resistant to ATRA or As$_2$O$_3$ alone. Further studies are required in order to explain the molecular basis of this synergism better.

G. Visani, P.P. Piccaluga, G. Martinelli, M. Rossi, M. Malagola, M. Baccarani
Correspondence: Giuseppe Visani, MD
Department of Hematology Muraglia, Via Lombroso 61100 Pesaro, Italy
Tel: +39-0721-364039 - Fax: +39-0721-364306

Figure 1. RT-PCR monitoring of minimal residual disease

References
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