

Combining retinoic acid and oral arsenic may be potentially the first-line therapy for non-high-risk acute promyelocytic leukemia

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Once regarded as a rapidly fatal disease, acute promyelocytic leukemia (APL) is now curable in most cases with the use of targeted treatment alone and without chemotherapy (CHT) (1). Platzbecker *et al.* (2) reported a prospective, randomized, multicenter, open-label, phase III noninferiority trial, which demonstrated the advantages of all-trans-retinoic acid (ATRA) and intravenous ATO over ATRA and CHT with significantly greater and more sustainable antileukemic efficacy over time for non-high-risk APL. The recent paper by Iland *et al.* (3) also revealed that ATRA and arsenic in initial therapy induction and consolidation for APL reduced the risk of relapse compared with historical controls. These studies demonstrated the advantages of combining ATRA and intravenous ATO over ATRA and CHT for non-high-risk APL.

On the other hand, Efficace *et al.* (4) reported that currently health-related quality-of-life (HRQOL) findings further supported the use of ATRA plus intravenous ATO as preferred first-line treatment in patients with non-high-risk APL. For this conclusion, Rahman commented (5): “*This is clinically meaningful, further supporting the use of ATRA plus arsenic as first-line treatment in patients with non-high-risk APL*”. This study demonstrated that use of ATRA plus intravenous ATO could give non-high-risk APL patients better quality of life compared with the treatment of ATRA and CHT.

Zhu *et al.* (6) has recently proposed that ATRA plus oral arsenic is not inferior to ATRA plus intravenous ATO as first-line treatment of APL and may be considered as a routine treatment option for appropriate patients. They have also reported excellent outcome in 20 patients with non-high-risk APL in a “largely home-based treatment protocol” and has shown that the treatment is effective, convenient, and economical (7). With regard to Zhu *et al.*'s protocol (7), Lo-Coco *et al.* (8) suggested that all patients with APL should be hospitalized and carefully monitored during the first 2 to 3 weeks of therapy to reduce the risk of early death. Once the platelet counts and coagulation function recovers and no sign of the differentiation syndrome, the patients could be monitored during outpatient treatment with close follow-up. This study indicates that the treatment of ATRA plus oral arsenic shows effective, convenient and economical, which is not inferior to ATRA plus intravenous ATO and has the potential to be first-line therapy of APL.

However, before ATRA and oral arsenic become the front-line therapy for non-high-risk APL, three issues are required to be explained here. First, in Zhu's trial (6), patients with APL were not rigorously stratified into non-high-risk and high-risk groups, and all the APL patients received three courses of CHT in consolidation phase. Thus, a prospective, randomized study is needed to show

whether ATRA and oral arsenic alone can be better than or equal to ATRA and intravenous ATO in non-high-risk patients in the future. Second, arsenic is an acknowledged carcinogen. As for the side effects of intravenous ATO, Hu *et al.* have reported long-term observation for intravenous ATO (9). However, oral arsenic is a formula containing tetra-arsenic tetra-sulfide and other three kinds of traditional Chinese medicine (6). The side effects, particularly the potential carcinogenesis of oral arsenic must be evaluated in the future before it becomes the first-line therapy for non-high-risk APL. Third, if ATRA and oral arsenic cause severe differentiation syndrome, or the white blood cell count sharply elevated during the induction therapy for non-high-risk APL, CHT would be taken to control those situations instead of ATRA and oral arsenic alone.

In summary, based on these current advances, ATRA and oral arsenic may become the standard treatment for non-high-risk APL patients. Of course, in the future, this conclusion must be confirmed by prospective, randomized studies and the side effects of oral arsenic must be evaluated. All APL patients should be hospitalized and carefully monitored during the first 2 to 3 weeks of therapy and CHT would be taken to control severe differentiation syndrome during the induction therapy.

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Footnote

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