PROCEEDINGS ARTICLE

Novel strategies in treatment of acute promyelocytic leukemia

F Lo-Coco^{1,2} and L Cicconi^{1,2}

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia characterized by t(15;17) and a life-threatening coagulopathy. Once highly fatal, nowadays standard treatment approaches with all-trans retinoic acid (ATRA) along with chemotherapy allows curing up to 80–85% of cases. In the past decade, arsenic trioxide used alone or in combination with ATRA has demonstrated high efficacy in APL, and is currently regarded as the gold standard for treatment of relapsed cases. Chemotherapy-free approaches based on the combination of arsenic trioxide and ATRA are currently being tested against standard ATRA and chemotherapy in randomized clinical trials for frontline therapy of APL.

Leukemia Supplements (2012) 1, S18–S19; doi:10.1038/leusup.2012.12

Keywords: acute promyelocytic leukemia; risk-adapted chemotherapy; ATRA; ATO

Acute promyelocytic leukemia (APL) has long since been regarded as the most malignant form of human leukemia. The disease is characterized by severe coagulopathy and hemorrhagic diathesis, which is responsible for high rates of early death. The mechanisms underlying this insidious complication are as yet not fully understood, and thus the APL coagulopathy still remains a great challenge despite the impressive advances in antileukemic treatment and overall prognostic outcome. The genetic hallmark of APL is a reciprocal balanced translocation t(15;17) that generates the fusion gene *PML-RARA*. This represents an extremely valuable biomarker whose rapid and sensitive detection through molecular assays is widely used to refine diagnosis and monitor response to treatment.

The introduction of anthracycline-based monochemotherapy by Bernard in 1973 was the first milestone in APL treatment, as it resulted in important improvements in complete remission (CR) rates. However, the condition of the majority of patients who entered CR, relapsed during follow-up, and no more than 30% of them were cured.¹

The introduction of differentiation treatment based on all-trans retinoic acid (ATRA) developed by Chinese investigators in Shanghai revolutionized APL treatment, leading in the mid '90s to the design of ATRA plus chemotherapy trials that were conducted in Europe, the United States and Japan by multicenter cooperative groups. The results of these studies, which were recently updated on a very long-term follow-up, indicate that the simultaneous use of ATRA and anthracycline-containing chemotherapy is the best option, as it can cure up to 80% of newly diagnosed patients.²

In the past decade, the Italian GIMEMA and the Spanish PETHEMA groups developed a risk-adapted approach based on a frontline relapse risk score for patients treated with AIDA-like regimens. This allowed avoiding unnecessary toxicity for patients with white blood cell counts less than $10 \times 10^9/l$, whereas more intensive post-induction chemotherapy including cytarabine was adopted for high-risk (hyperleukocytic) patients. The results of both GIMEMA and PETHEMA studies using a risk-adapted approach showed significant improvement of outcome, resulting in CR rates of up to 95% and overall survival rates of >85%.^{3,4}

In the late '90s, studies published by investigators at Harbin Medical University in Shanghai showed the high efficacy of an arsenic compound, arsenic trioxide (ATO), as a single agent in the treatment of relapsed APL.⁵ Subsequent studies in Europe, the United States, India and Iran confirmed these observations, and ATO is currently regarded as the best treatment option in relapsed patients. In parallel, several trials were started to explore the role of ATO in newly diagnosed patients.⁵

Several studies have demonstrated at the molecular level the synergistic action of ATO and ATRA in inducing differentiation and apoptosis of APL blasts through enhanced *PML-RARA* degradation. A Chinese study by Shen *et al.*,⁶ published in 2004, compared for the first time the outcome of 6 patients treated, respectively, with ATRA, ATO and the combination of the two compounds with a comparable CR rate among the three groups (>90%), but a significantly longer CR in the ATO plus ATRA group. The ATRA plus ATO combined approach is currently being tested in two ongoing randomized trials conducted by the Italian–German groups GIMEMA-SAL-ALSG (APL0406) and by the British NCRI. Both trials are comparing a totally chemotherapy-free approach (experimental arm) against the standard AIDA-like regimen. In particular, the Italian–German study investigates in the experimental arm the efficacy of the prolonged ATO + ATRA scheme developed by Estey *et al.* in 2006,⁷ together with longitudinal PCR monitoring as a safety criterion to adopt preemptive salvage for patients who undergo molecular relapse. Until the results of these trials are available, ATO should be restricted to patients included in clinical trials and in those patients in whom there are contraindications to chemotherapy.

The role of ATO as a single agent or in combination is currently being explored in consolidation therapy as well. In particular, a recent large, randomized study by the US Intergroup showed significant improvements in event-free and overall survival for patients receiving two courses of ATO (that is, 5 days a week for 5 weeks in each cycle) given after CR and before the standard post-remission regimen (that is, ATRA plus chemotherapy), as compared with those receiving only ATRA plus chemotherapy consolidation.

¹Department of Biopathology, University of Rome "Tor Vergata", Rome, Italy and ²Laboratorio di Neuro-Oncoematologia, Fondazione Santa Lucia, Rome, Italy. Correspondence: Professor F Lo-Coco, Department of Biopathology, University of Rome "Tor Vergata", Via Montpellier 1, Rome 00133, Italy. E-mail: francesco.lo.coco@uniroma2.it

In addition, the French–Belgian–Swiss and the PETHEMA-HOVON groups are evaluating the role of ATO in consolidation treatment in two ongoing studies.⁸

The former randomization will test, as a primary objective, the role of cytarabine, ATRA and ATO in combination with idarubicin in patients younger than 70 years with white blood cells less than $10 \times 10^9/l$, whereas the latter will assess the efficacy of two courses of ATO given immediately after CR and just before standard consolidation therapy.

The upcoming results of all the mentioned randomized studies should soon clarify the role of ATO in frontline management of APL.

CONFLICT OF INTEREST

FL-C received speaker's honoraria from Cephalon. LC declares no conflict of interest.

This article was published as part of a supplement that was supported by Novartis, MSD Italia, Roche, Celgene, GlaxoSmithKline, Sanofi, Gilead, Adienne, Italfarmaco, Pierre Fabre Pharmaceuticals with an unrestricted educational contribution to AREO—Associazione Ricerche Emato-Oncologiche (Genoa) and AMS—Associazione Malattie del Sangue (Milan) for the purpose of advancing research in acute and chronic leukemia.

REFERENCES

- 1 Bernard J. History of promyelocytic leukaemia. *Leukemia* 1994; **8** (Suppl 2): S1–S5.
- 2 Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. *Blood* 2008; **111**: 2505–2515.
- 3 Sanz MA, Montesinos P, Vellenga E, Rayón C, de la Serna J, Parody R *et al*. Risk-adapted treatment of acute promyelocytic leukemia with all-trans retinoic acid and anthracycline monotherapy: long-term outcome of the LPA 99 multicenter study by the PETHEMA Group. *Blood* 2008; **112**: 3130–3134.
- 4 Lo-Coco F, Avvisati G, Vignetti M, Breccia M, Gallo E, Rambaldi A, *et al*, Italian GIMEMA Cooperative Group. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. *Blood* 2010; **116**: 3171–3179.
- 5 Zhang P, Wang SY, Hu LH. Arsenic trioxide treated 72 cases of acute promyelocytic leukemia. *Chin J Hematol* 1996; **17**: 58–62.
- 6 Shen ZX, Shi ZZ, Fang J, Gu BW, Li JM, Zhu YM *et al*. All-trans retinoic acid/As2O3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. *Proc Natl Acad Sci USA* 2004; **101**: 5328–5335.
- 7 Estey E, Garcia-Manero G, Ferrajoli A, Faderl S, Verstovsek S, Jones D *et al*. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. *Blood* 2006; **107**: 3469–3473.
- 8 Sanz MA, Lo-Coco F. Modern approaches to treating acute promyelocytic leukemia. *J Clin Oncol* 2011; **29**: 495–503.