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

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.[1,2] Given its high efficacy in inducing durable molecular remission (CRm), ATO is considered the most active single agent in APL and is currently also being 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 randomized studies are available which offer concrete support for given consolidation (allo-HSCT, auto-SCT, further ATO or chemotherapy). In spite of this, most investigators would nowadays recommend proceeding to HSCT after re-induction of CR.[1,2] 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 first 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.[3] 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) in Rome. The main clinico-biological features and treatment outcomes of the 9 patients are shown in Table 1. Two patients (UPN 5 and UPN 6) have been reported previously.[4,5] At time of ATO/ATRA initiation, 7 patients were in first molecular relapse whereas UPN 8 and 9 were in second hematologic and second molecular relapse, respectively. The median time of molecular or hematologic first CR duration was 1.9 years (range 1-7). All patients received ATO/ATRA according to the schedule reported by Estey *et al.*[3] 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 this prolonged therapy and not offered an HSCT option because of long first 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 one (n=2) or 2 cycles (n=7). Two patients experienced mild toxicity during re-induction therapy consisting of transient QTc prolongation and grade 2 neutropenia, respectively, requiring temporary discontinuation of ATO. Another patient treated for molecular relapse experienced electrolyte abnormalities with no QTc prolongation which was corrected by electrolyte replacement and did not require discontinuaton of the drug. Only 2 patients required hospitalization one for treatment of 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 second CRm for a median time of 25 months (range 11-50) and one (UPN 1) underwent second molecular relapse during PCR monitoring at ten months after initiation of ATO-based salvage therapy (Table 1). The latter patient received allogeneic HSCT and is currently in third CR. Though limited to a small number of patients, our observation suggests that prolonged

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

UPN	Sex/age*	FAB	WBC ($x10^9$/L)	Relapse risk	Previous treatments	Duration of previous CR(s)	Disease status at time of ATO+ATRA initiation	Toxicity during ATO + ATRA	Outcome
1	M/51	M3	2.5	Low	AIDA§	15 months	1st molecular relapse	no	relapsed at 10 mos
2	M/54	M3	3.5	Interm	AIDA	12 months	1st molecular relapse	QTc prolongation	CRm^ (22+ mos)
3	F/46	M3	4.2	Interm	AIDA	32 months	1st molecular relapse	no	CRm (28+ mos)
4	F/70	M3	5.1	Interm	AIDA	28 months	1st molecular relapse	no	CRm (18+ mos)
5	M/38	M3	1.0	Interm	AIDA	84 months	1st EM° and molecular relapse	no	CRm (39+ mos)
6	F/32	M3	4.2	Interm	AIDA	48 months	1st molecular relapse	no	CRm (50+ mos)
7	M/61	M3v	9.5	Interm	AIDA	17 months	1st molecular relapse	electrolyte abnormalities	CRm (14+ mos)
8	M/69	M3	1.8	Low∞	AIDA/GO# + ATRA	22 months/ 12 months	2nd hematologic relapse	no	CRm (31+ mos)
9	M/52	M3	11	High	AIDA/ARA-C + MTZ@	17 months/ 13 months	2nd molecular relapse	neutropenia (grade 2)	CRm (11+ mos)

**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. ∞high relapse risk at second relapse. NA° Not available.*

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 to refuse HSCT and advanced age in some cases, was the 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.[6] On the other hand, a recent update of the Estey study[3] which first reported this regimen in newly diagnosed patients, demonstrated considerable efficacy with excellent outcome in particular for non-high risk APL.[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,[5] and her second CR currently already exceeds the duration of first 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 second molecular CR. In that study, relapses were hematologic in 12 cases and molecular in one case. All patients were treated with chemotherapy and after consolidation all achieved CRm: 10 of 13 patients (77%) were alive and well after a median follow up of 25 months from second CR[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.

Massimo Breccia,[1] Laura Cicconi,[1] Clara Minotti,[1] Roberto Latagliata,[1] Laura Giannì,[2] and Francesco Lo-Coco[1]

[1]Department of Cellular Biotechnologies and Hematology, Sapienza University, Rome; and [2]Department of Biopathology, University Tor Vergata, and Laboratory of Neuro-Oncohematology, Santa Lucia Foundation, Rome, Italy.

Correspondence: Massimo Breccia, MD, Dept. of Human Biotechnologies and Hematology, Via Benevento 6, 00161 Roma, Italy. Phone: international + 39.06.857951. Fax: international +39.06.44241984. E-mail: breccia@bce.uniroma1.it

Key words: ATRA, combined arsenic trioxide, prolonged therapy, relapse, acute promyelocytic leukemia.

Citation: Breccia M, Cicconi L, Minotti C, Latagliata R, Giannì L, and Lo-Coco F. Efficacy of prolonged therapy with combined arsenic trioxide and ATRA for relapse of acute promyelocytic leukemia. Haematologica 2011; 96(9):1390-1391. doi:10.3324/haematol.2011.045500

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

References

1. Sanz MA, Lo Coco F. Modern approaches to treating acute promyelocytic leukemia. J Clin Oncol. 2011;29(5):495-503.
2. Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH, et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2009;113(9):1875-91.
3. 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(9):3469-73.
4. Pacilli L, Lo Coco F, Ramadan SM, Giannì L, Pingi A, Remotti D, et al. Promyelocytic sarcoma of the spine: a case report and review of the literature. Adv Hematol. 2010; 2010:137608.
5. Ammatuna E, Cavaliere A, Divona M, Amadori S, Scambia G, Lo Coco F. Successful pregnancy after arsenic trioxide therapy for relapsed acute promyelocytic leukemia. Br J Haematol. 2009; 146(3):341.
6. Raffoux E, Rousselout P, Poupon J, Daniel MT, Cassinat B, Delarue R, et al. Combined treatment with arsenic trioxide and all-trans-retinoic acid in patients with relapsed acute promyelocytic leukemia. J Clin Oncol. 2003;21(12):2326-34.
7. Ravandi F, Estey E, Jones D, Faderl S, O'Brien S, Fiorentino J, et al. Effective treatment of acute promyelocytic leukemia with all-trans retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. J Clin Oncol. 2009;27(4):504-10.
8. Ferrara F, Finizio O, Izzo T, Riccardi C, Criscuolo C, Carbone A, et al. Autologous stem cell transplantation for patients with acute promyelocytic leukemia in second molecular remission. Anticancer Res. 2010;30(9):3845-9.

Allogeneic hematopoietic stem cell transplantation for isolated and leukemic myeloid sarcoma in adults: a report from the Acute Leukemia Working Party of the European group for Blood and Marrow Transplantation

Myeloid sarcoma (MS), also known as granulocytic sarcoma or chloroma, is a rare extramedullary tumor composed of immature myeloid cells at different stages of differentiation which can involve any site of the body. Most cases of myeloid sarcoma will develop within the first year preceding the occurrence of acute myeloid leukemia (AML), or concomitantly to AML, or at relapse of AML. More rarely, myeloid sarcoma could also be observed in the setting of myelodysplastic syndrome or myeloproliferative neoplasms, or as an isolated myeloid sarcoma (also designated as *de novo*, non-leukemic or primary MS).[1] Common practice suggests that patients with isolated myeloid sarcoma should receive AML-like induction chemotherapy.[2] Although a single comparative study has previously shown that isolated myeloid sarcoma may be associated with superior event-free survival and overall survival as compared to AML when patients receive AML-type therapy,[3] the outcome of such patients is considered poor; median survival is less than 24 months[4-6] The best therapeutic option has not yet been established. Recently, we and others have shown that allogeneic hematopoietic stem cell transplantation (allo-HSCT) may represent a valid treatment option in leukemic myeloid sarcoma.[7,8] However, it is still unclear whether allo-HSCT is also a good option for patients with isolated myeloid sarcoma.

To assess the role of allo-HSCT in patients with isolated myeloid sarcoma and compare the outcome of such patients with leukemic myeloid sarcoma patients, we performed a retrospective multicenter study assessing the results of allo-HSCT in 99 patients reported to the EBMT registry between January 1991 and June 2009 with isolated (n=30) or leukemic (n=69) myeloid sarcoma. Patients' characteristics and information regarding disease and transplant are summarized in Table 1. The previously published outcome of adult patients[8] was updated for this