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

Table 1. Patients', disease and transplant characteristics.

Characteristics	Overall cohort n=99	Isolated myeloid sarcoma n=30	Leukemic myeloid sarcoma n=69	*P* value (a)
Gender, male recipient	57 (57%)	18 (60%)	39 (56%)	0.75
Median age, years (range)	40 (18-69)	40 (18-69)	39 (18-69)	0.69
Median year of transplant (range)	2004 (1991-2009)	2005 (1991-2009)	2003 (1991-2009)	0.03
Interval between diagnosis and allo-HSCT, days (range)		216 (86-1090)	190 (78-3575)	0.36
FAB classification				
Known(b)			51	
Unknown			18	
Cytogenetic risk group(c)				
Favorable	16 (22%)	3 (21%)	13 (22%)	
Intermediate	48 (65%)	9 (64%)	39 (65%)	0.99
High-risk	10 (13%)	2 (14%)	8 (13%)	
Missing data	25	16	9	
CNS involvement				
Yes/no/missing data	12/51/36	1/18/11	11/33/25	
Localizations				
Single site(d)	35	11	24	
>= 2 sites(e)	15	7	8	
Unknown	49	12	37	
In conjunction with AML			45	
Before AML diagnosis			10	
After AML diagnosis			6	
Unknown			8	
Status at transplant				
First CR	52 (52%)	14 (47%)	38 (55%)	
Second CR or beyond	28 (28%)	7 (23%)	21 (30%)	0.20
Advanced, refractory or persistent disease:	19 (20%)	9 (30%)	10 (15%)	
Primary refractory	10	5	5	
First relapse	9	4	5	
Donor type				
HLA-identical sibling	69 (70%)	21 (70%)	48 (70%)	0.97
HLA-matched unrelated donor	30 (30%)	9 (30%)	21 (30%)	
Stem cell source				
Bone marrow	37 (37%)	9 (30%)	28 (41%)	
PBSC	60 (61%)	21 (70%)	39 (57%)	0.35
Cord blood	2 (2%)	0	2 (3%)	
Patient CMV serostatus				
Negative	36 (39%)	9 (36%)	27 (40%)	
Positive	56 (61%)	16 (64%)	40 (60%)	0.71
Unknown	7	5	2	
Donor CMV serostatus				
Negative	44 (48%)	16 (59%)	28 (36%)	
Positive	47 (52%)	11 (41%)	36 (56%)	0.18
Unknown	8	3	5	
Type of conditioning regimen				
Standard myeloablative	79 (80%)	24 (80%)	55 (80%)	
RIC	20 (20%)	6 (20%)	14 (20%)	0.97
TBI/CY	52	12	40	
BU/CY	22	10	12	
Other myeloablative	5	2	3	
RIC with TBI	6	0	6 (2 Grays)	
RIC with no TBI	14	6	8	

AML: acute myeloid leukemia; CNS: central nervous system; CR: complete remission; PBSC: peripheral blood stem cells; CMV: cytomegalovirus; RIC: reduced intensity conditioning; TBI: total body irradiation; CY: cyclophosphamide; BU: busulfan. [a]P: comparison between isolated and leukemic myeloid sarcoma patients. [b]M0: n=2; M1: n=9; M2: n=15; M3: n=1; M4: n=8; M5: n=16. [c]Cytogenetic analyses have been performed by FISH in the isolated MS sub-group. [d]Isolated MS: skin n=6; soft tissue n=2; testis/ovary n=1; pleural n=1; oral cavity n=1; leukemic MS: skin n=7; soft tissue n=3; bone n=3; testis/ovary n=2; digestive tract n=3; eyes n=2; kidney n=1; oral cavity n=1; lymph nodes n=1; epidural n=1. [e]Isolated MS: skin and oral cavity n=1; testis/ovary and pleural n=1; heart, pleural and mediastinum n=1; lymph nodes and mediastinum n=1; lymph nodes, digestive tract and bone n=1; bone and jaw n=1; eyes, bone and kidney n=1. Leukemic MS: liver and lymph nodes n=1; skin and soft tissue n=2; skin and sinus n=1; skin and oral cavity n=1; lymph nodes, soft tissue and heart n=1; breast and eyes n=1; breast and kidney n=1.

Table 2. Comparison of outcomes between isolated myeloid sarcoma and leukemic myeloid sarcoma.

Outcomes	Overall cohort n=99	Isolated myeloid sarcoma n=30	Leukemic myeloid sarcoma n=69	P*
Engraftment	99 (100%)	30 (100%)	69 (100%)	
Time to ANC≥0.5×10⁹/L, days (range)		15 (11-30)	18.5 (9-49)	
Acute GVHD				
Grade 2-4	23%	27%	35%	
Grade 3-4	9%	3%	11%	
2-year CI of Chronic GVHD	45±5%	54±11%	41±7%	0.38
5-year OS	48±6% Median: 39 months	33±13%	51%±7%	0.63
5-year LFS				
Overall	36±5% Median: 17 months	30±9%	37±6%	0.45
5-year CI of relapse	40±4%	45±10%	38±6%	0.64
5-year CI of NRM	19±4%	17±5%	19±7%	0.76
Deaths	48	15	33	
Causes of death				
Relapse/progression	27	9	18	
Multiple organ failure	2		2	
Infections	7	1	6	
Hemorrhage	1		1	
Interstitial pneumonitis	5	1	4	
GVHD	4	2	2	
Cardiac toxicity	1	1		
Missing data	1	1		
Relapses**	42	13	29	
As AML	8	2	6	
As myeloid sarcoma	10	5	5	
As both	6	2	4	
Missing data	28	4	14	
Relapses according to conditioning regimen				
Myeloablative	33	9	24	
RIC	9	4	5	

*GVHD: graft-*versus*-host disease; CI: cumulative incidence; OS: overall survival; LFS: leukemia-free survival; CR: complete remission; NRM: non-relapse mortality, AML: acute myeloid leukemia; RIC: reduced intensity conditioning; MS: myeloid sarcoma. *P value: comparison between isolated and leukemic myeloid sarcoma patients. **Considering patients with relapse as MS or MS+AML (n=16), 6 MS relapses occurred at the original site while 10 occurred at a different site.*

study. Median follow up was 48 months (range 6-213 months). There were no significant statistical differences between the two groups except year of allo-HSCT. Study end points were the probabilities of overall survival, leukemia-free survival (LFS), relapse incidence (RI), non-relapse mortality (NRM) and chronic graft-*versus*-host disease. Statistical analyses were performed using SPSS 18.0 (SPSS Inc, Chicago, IL) and Splus 8.1 (Math-Soft Inc, Seattle, WA) packages.

Overall results and comparison of outcomes between isolated and leukemic myeloid sarcoma are given in Table 2. Some patients in the leukemic group had received a second allo-transplant in the leukemic group, and could achieve a second persistent complete remission (CR) as previously reported.[8] As outcomes of isolated and leukemic myeloid sarcoma were found to be similar, data for the two groups were pooled to perform univariate and multivariate analyses. Thus, considering the whole cohort (n=99), in univariate analysis, factors associated with higher leukemia-free survival and lower relapse incidence were: CR status at transplant (5-year LFS: 40±6% *vs.*16±8%; *P*<0.0001; 5-year RI: 39±6% *vs.* 68±11%; *P*=0.0009) and cytogenetics (5-year LFS: good 50±13% *vs.* intermediate 30±7% *vs.* poor 20±13%, *P*=0.06; 5-year RI: good 37±13% *vs.* intermediate 43±8% *vs.* poor: 70±16%, *P*=0.05). The only factor associated with higher non-relapse mortality was patient gender (male: 27±6% *vs.* female: 10±5%, *P*=0.04). In multivariate analysis, high-risk cytogenetics remained significantly associated with poorer leukemia-free survival and increased relapse incidence (HR=2.55, 95%CI: 1.14-5.73, *P*=0.02; HR=2.64, 95%CI: 1.05-6.63, *P*=0.04, respectively), while a CR status at transplant was associated with improved leukemia-free survival (HR=0.44, 95%CI: 0.22-0.88, *P*=0.02). There was a trend for a lower incidence of relapse for patients in complete remission (HR=0.49, 95%CI: 0.22-1.07, *P*=0.07).

This study included the largest series of isolated myeloid sarcoma patients having undergone allo-HSCT reported so far. With a 5-year overall survival and leukemia-free survival of 48% and 36%, respectively, this study suggests that allo-HSCT is a potentially efficient treatment for isolated myeloid sarcoma with relatively acceptable toxicity (overall 5-year NRM 17%). When

comparing isolated and leukemic myeloid sarcoma, there were no significant differences in term of outcomes. The multivariate analysis showed that CR status at transplant was associated with improved leukemia-free survival while high-risk cytogenetics reduced the chance of long-term leukemia-free survival. If the former result is expected, the latter should be taken with caution, as cytogenetic data were missing in most cases of isolated myeloid sarcoma.

We think our results support the use of allo-HSCT as first-line therapy for myeloid sarcoma, especially in patients achieving complete remission after AML-type therapy, since one should bear in mind that the prognosis of myeloid sarcoma is generally poor with an overall survival of usually less than two years in patients not receiving allo-HSCT.[4-6] The latter is in line with recent guidelines from Dohner *et al.*,[2] recommending the use of AML-like induction therapy for myeloid sarcoma, followed by consolidation before proceeding to allo-HSCT. Also, involved field radiation therapy may be considered to improve management of localized tumors.

Besides cytogenetics, the role of new molecular prognostic markers such as NPM1 or FLT3-ITD mutations in myeloid sarcoma should also be investigated, as they will likely influence outcome after chemotherapy and/or allo-HSCT.[9] Interestingly, a case report regarding one patient with FLT3-ITD positive myeloid sarcoma suggested a beneficial effect of the kinase inhibitor sorafenib.[10]

We conclude that allo-HSCT is an effective treatment for patients with myeloid sarcoma. Patients with isolated or leukemic myeloid arcoma have similar outcomes after allo-HSCT. While prospective evaluations are needed, allo-HSCT could be considered the optimal therapy for both isolated and leukemic myeloid sarcoma.

Patrice Chevallier,[1] Myriam Labopin,[2] Jan Cornelissen,[3] Gérard Socié,[4] Vanderson Rocha,[2] and Mohamad Mohty[1,2] on behalf of the ALWP of EBMT

[1]Service d'Hématologie Clinique, CHU Hôtel Dieu, Université de Nantes, Centre d'Investigation Clinique en Cancerologie (CI2C) and INSERM U892, Nantes, France; [2]ALWP, EBMT-Paris Office, Hôpital Saint Antoine AP-HP, Université Pierre et Marie Curie Paris 6, UMR-S 893 Equipe 14, Paris, France; [3]Erasmus MC-Daniel den Hoed Cancer Centre, Rotterdam, The Netherlands, and [4]Hôpital Saint-Louis, Department of Hematology-BMT, Paris, France

Correspondence: Patrice Chevallier, MD, Service d'Hématologie Clinique, CHU de Nantes, Place A. Ricordeau, 44093 Nantes Cedex, France. Phone: international +33.240083271. Fax: international +33.240083250. E-mail: patrice.chevallier@chu-nantes.fr

Key words: Allo-HSCT, myeloid sarcoma, AML, ALWP, EBMT.

Acknowledgments: we thank all the data managers, especially Benedicte Samey, from the different EBMT participating centers for data management and collection. We also thank co-investigators of the study who recruited patients, provided clinical care, and commented on the manuscript: G Sucak, P Ljungman, B Lioure, J Finke, R Tabrizi, N Contentin, A Gratwohl, L Volin, M Michallet, JP Vernant, JO Bay, I Yakoub-Agha and Arnon Nagler.

Citation: Chevallier P, Labopin M, Cornelissen J, Socié G, Rocha V, and Mohty M on behalf of the ALWP of EBMT. 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. Haematologica 2011; 96(9):1391-1394. doi:10.3324/haematol.2011.041418

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. Campidelli C, Agostinelli C, Stitson R, Pileri SA. Extramedullary manifestation of myeloid disorders. Am J Clin Pathol. 2009;132 (3):426-37.
2. Döhner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115(3):453-74.
3. Tsimberidou AM, Kantarjian HM, Wen S, Keating MJ, O'Brien S, Brandt M, et al. Myeloid sarcoma is associated with superior event-free survival and overall survival compared with acute myeloid leukmia. Cancer. 2008;113(6):1370-8.
4. Byrd JC, Edenfield WJ, Shields DJ, Dawson NA. Extramedullary myeloid cell tumors in acute nonlymphocytic leukemia: a clinical review. J Clin Oncol. 1995;13(7):1800-16.
5. Yamauchi K, Yasuda M. Comparison in treatments of non-leukemic granulocytic sarcoma: report of two cases and a review of 72 cases in the literature. Cancer. 2002;94(6):1739-46.
6. Tsimberidou AM, Kantarjian HM, Estey E, Cortes JE, Verstovsek S, Faderl S, et al. Outcome in patients with nonleukemic granulocytic sarcoma treated with chemotherapy with or without radiotherapy. Leukemia. 2003;17(6):1100-3.
7. Pileri SA, Ascani S, Cox MC, Campidelli C, Bacci F, Piccioli M, et al. Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. Leukemia. 2007;21(2):340-50.
8. Chevallier P, Mohty M, Lioure B, Michel G, Contentin N, Deconinck E, et al. Allogeneic hematopoietic stem-cell transplantation for myeloid sarcoma: a retrospective study from the SFGM-TC. J Clin Oncol. 2008;26(30):4940-3.
9. Falini B, Lenze D, Hasserjian R, Coupland S, Jaehne D, Soupir C, et al. Cytoplasmic mutated nucleophosmin (NPM) defines the molecular status of a significant fraction of myeloid sarcomas. Leukemia. 2007;21(7):1566-70.
10. Choschzick M, Bacher U, Ayuk F, Lebeau A. Immunohistochemistry and molecular analyses in myeloid sarcoma of the breast in a patient with relapse of NPM1-mutated and FLT3-mutated AML after allogeneic stem cell transplantation. J Clin Pathol. 2010;63(6):558-61.